JULY 1973 · VOL. 178, NO. 1
ANSUA5

COK-H01448-5-P024764

ANNALS of SURGERY

A Monthly Review of
Surgical Science and Practice
Since 1885

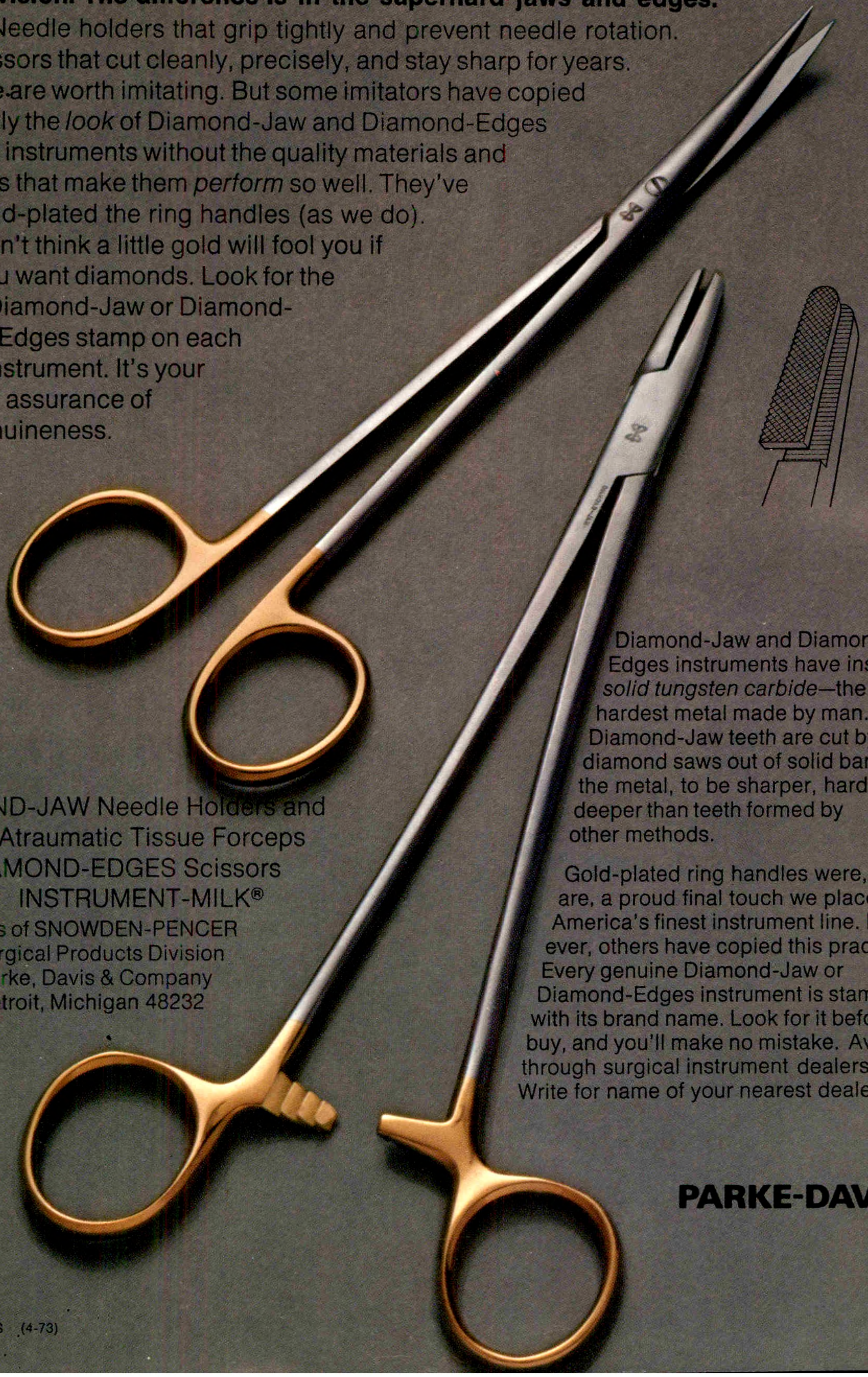
5

J. B. LIPPINCOTT COMPANY

Don't mistake gold for diamonds

There is only one true line of DIAMOND-JAW® and DIAMOND-EDGES® instruments, made by our Snowden-Pencer Medical-Surgical Products Division. The difference is in the superhard jaws and edges.

Needle holders that grip tightly and prevent needle rotation. Scissors that cut cleanly, precisely, and stay sharp for years. These are worth imitating. But some imitators have copied only the *look* of Diamond-Jaw and Diamond-Edges instruments without the quality materials and processes that make them *perform* so well. They've gold-plated the ring handles (as we do). But we don't think a little gold will fool you if you want diamonds. Look for the Diamond-Jaw or Diamond-Edges stamp on each instrument. It's your assurance of genuineness.



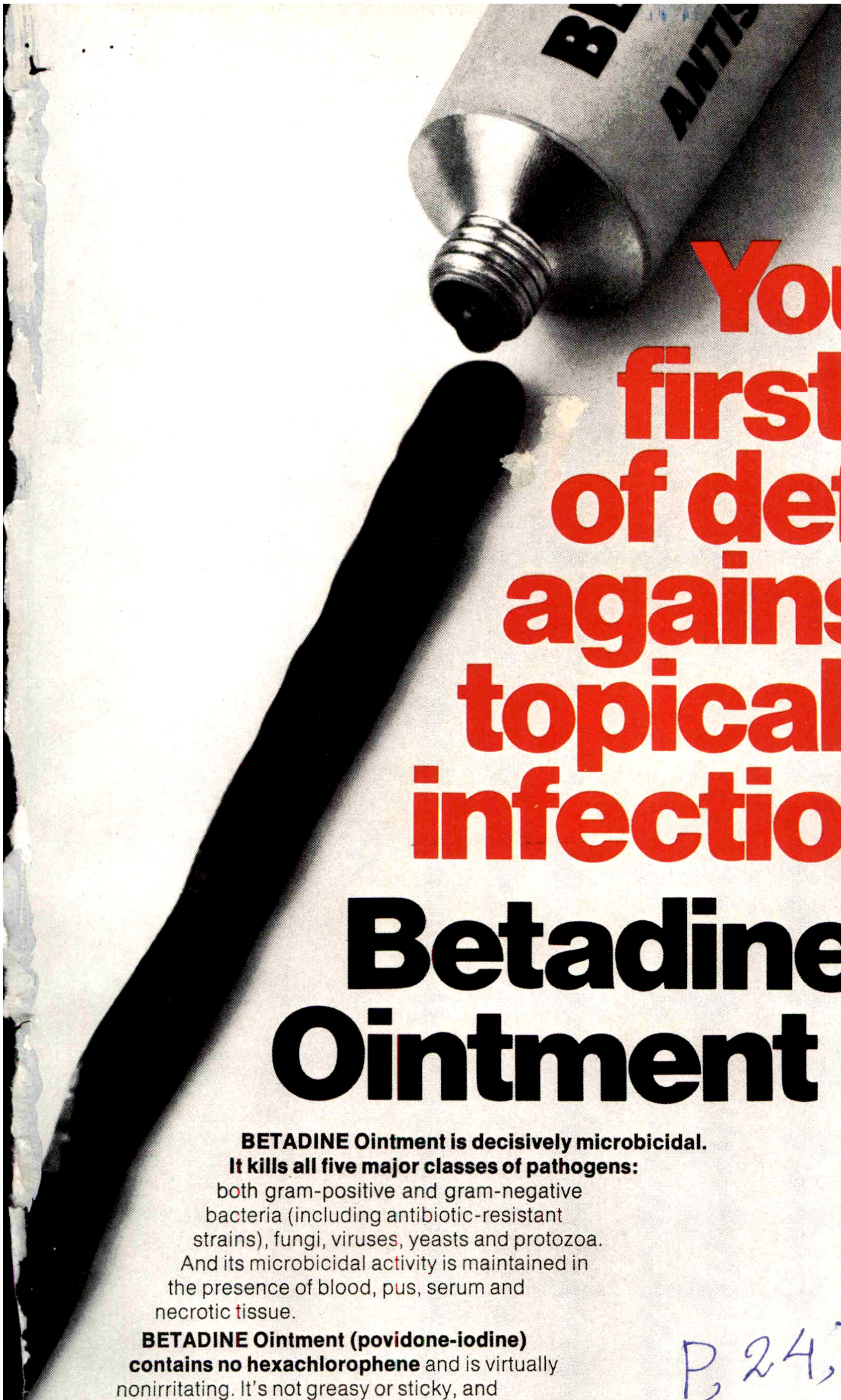
Diamond-Jaw and Diamond-Edges instruments have inserts of *solid tungsten carbide*—the hardest metal made by man. Diamond-Jaw teeth are cut by diamond saws out of solid bars of the metal, to be sharper, harder, deeper than teeth formed by other methods.

Gold-plated ring handles were, and still are, a proud final touch we place on America's finest instrument line. However, others have copied this practice. Every genuine Diamond-Jaw or Diamond-Edges instrument is stamped with its brand name. Look for it before you buy, and you'll make no mistake. Available through surgical instrument dealers. Write for name of your nearest dealer.

DIAMOND-JAW Needle Holders and
Atraumatic Tissue Forceps
DIAMOND-EDGES Scissors
INSTRUMENT-MILK®
Products of SNOWDEN-PENCER
Medical-Surgical Products Division
Parke, Davis & Company
Detroit, Michigan 48232

PARKE-DAVIS

PD-JA-0937-1-MS (4-73)



Your first line of defense against topical infections

Betadine Ointment

5

P, 24,764

BETADINE Ointment is decisively microbicidal. It kills all five major classes of pathogens: both gram-positive and gram-negative bacteria (including antibiotic-resistant strains), fungi, viruses, yeasts and protozoa. And its microbicidal activity is maintained in the presence of blood, pus, serum and necrotic tissue.

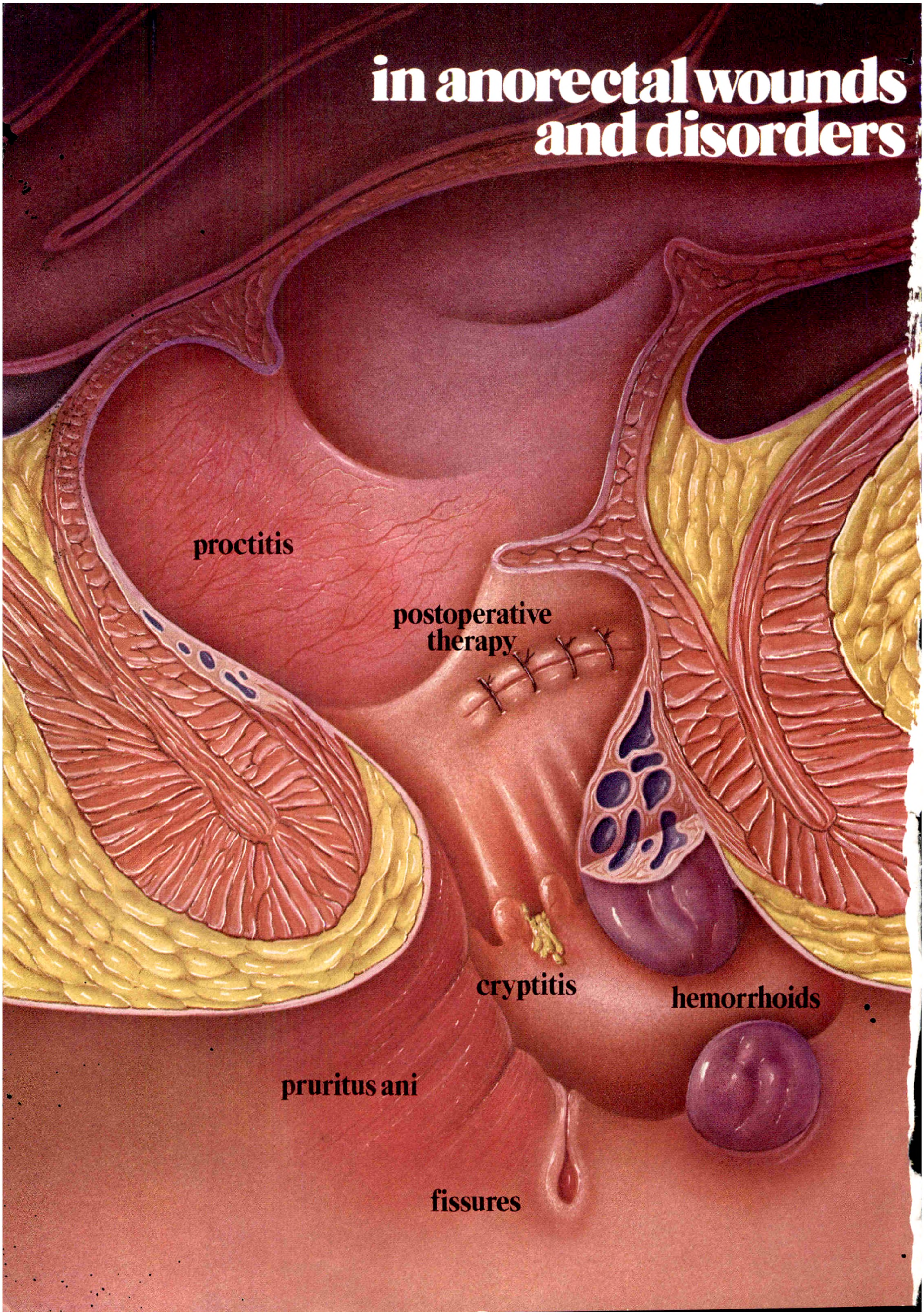
BETADINE Ointment (povidone-iodine) contains no hexachlorophene and is virtually nonirritating. It's not greasy or sticky, and easily washes off skin or natural fabrics. The application site can be bandaged.

Supplied in ⅛-oz. pouchettes, 1-oz. tubes and 16-oz. (1 lb.) jars.

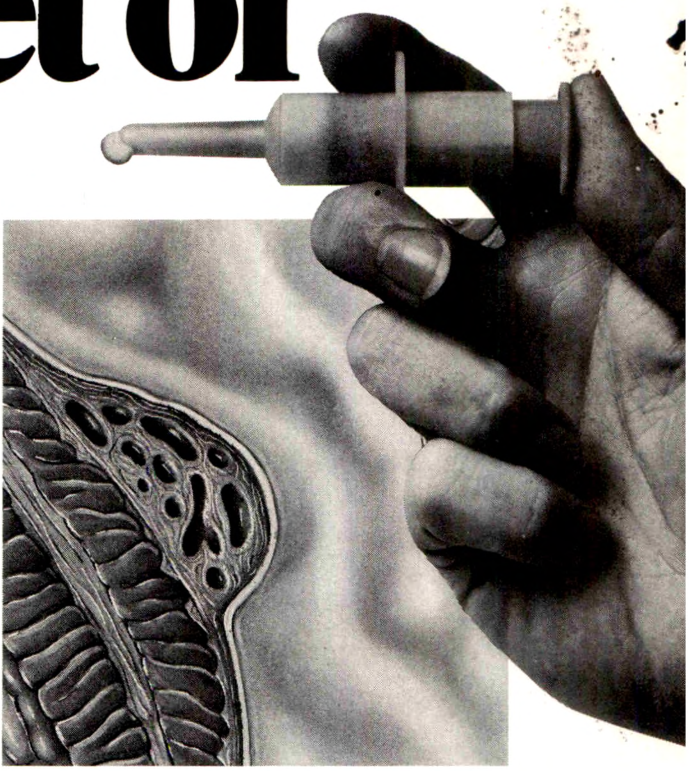
Purdue Frederick

©COPYRIGHT 1972, THE PURDUE FREDERICK COMPANY/NORWALK, CONN. 06856 B6735 124173

BETADINE "SECURITY ZONE" · APOLLO LUNAR MISSION


in anorectal wounds
and disorders
proctitis
postoperative
therapy
cryptitis
hemorrhoids
pruritus ani
fissures

...Blanket of Relief



Proctofoam®-HC, unique mucoadhesive foam, medicates the anorectal mucosa more rapidly and thoroughly than suppositories[1-6]

- better contact with the involved tissues;[1-6] spreads evenly throughout anal canal, rectal crypts, papillae and hemorrhoidal sites.
- unlike suppositories, won't "bypass" areas of pathology often missed by creams and suppositories.[1,4,5,6]
- unlike suppositories[5]—spreads evenly, with no need to melt.

Proctofoam-HC offers greater promise of a short and pain-free postoperative period

- faster wound healing[1-3,5] (2½ to 3 weeks instead of the expected 3½ to 4 weeks).[5]
- less scar formation—wounds more pliable, with clean, healthy-looking, granulating tissue.[1-3]
- less edema, inflammation, swelling, itching, pain and tenesmus.[1,3,5,6]
- preferred by patients over other forms of therapy.[1,4,5]

Compared to suppositories, roctofoam-HC provides greater patient comfort, convenience and economy

- measured-dose applicator facilitates self-administration with minimal discomfort[1] and eliminates finger contact with perianal area.
- mucoadhesive foam won't leak or stain.[2,4]
- foam container requires no refrigeration.
- less than half the cost of hydrocortisone-containing suppositories per application.

unique mucoadhesive foam

Proctofoam®-HC

Each measured dose (approx. 6.5 ml.) delivers hydrocortisone acetate 1%, pramoxine hydrochloride 1%, in a water-soluble, mucoadhesive foam base.

antiinflammatory/antipruritic/analgesic

References: 1. Bernstein, I.: *Surg. Dig. 4*:23, Jan. 1969. **2.** Sladek, W. R.: Scientific Exhibit, 69th Annual Meeting of American Proctologic Society, April 1970. **3.** Sladek, W. R.: *Amer. J. Clin. Res. 1*:33, Jan.-Feb. 1970. **4.** O'Brien, J. R.: *Surg. Dig. 4*:27, April 1969. **5.** Miller, H.: *Amer. J. Proctol. 18*:59, Feb. 1967. **6.** Lieberman, W.: *Amer. J. Proctol. 20*:134, April 1969.

Active Ingredients: Hydrocortisone acetate, 1%, and pramoxine hydrochloride, 1%, in a mucoadhesive foam base.

Indications: Temporary relief of anorectal inflammation, pruritus, pain and swelling associated with hemorrhoids, proctitis, cryptitis, fissures, postoperative pain and pruritus ani.

Contraindications: Abscess, extensive fistulas or sinus tracts, tuberculosis, varicella, vaccinia or acute herpes simplex.

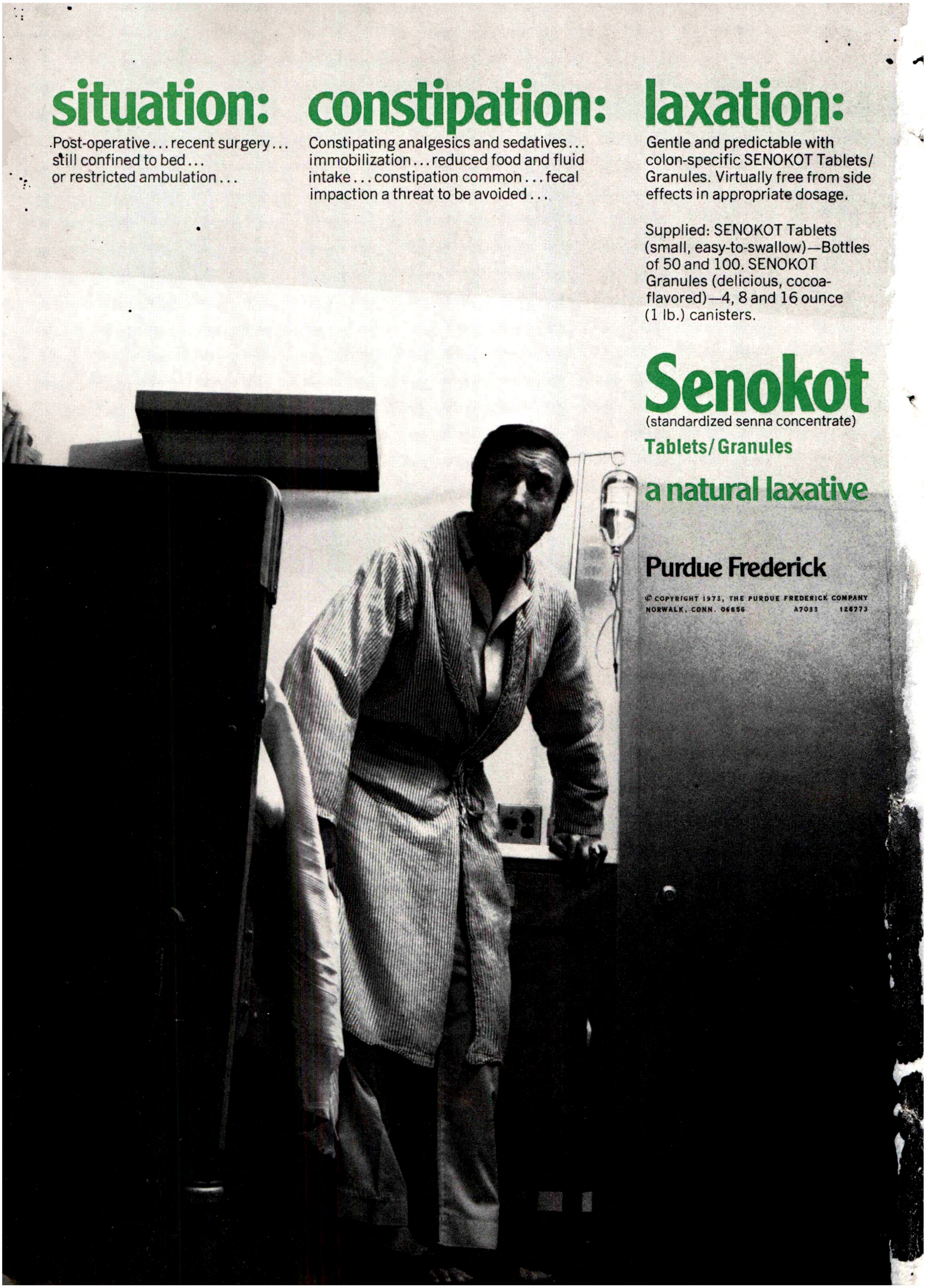
Precautions: A complete rectal examination to rule out serious pathology should be completed before instituting therapy. Do not use on infected lesions unless accompanied by antiinfective agents. Discontinue use if sensitivity develops.

Caution: Do not insert any part of the aerosol container into the anus. Contents of the container are under pressure, but not flammable.

Dosage: One applicatorful two or three times daily and after each bowel evacuation. Perianally, apply as needed.

How Supplied: In aerosol container providing 15 Gms. of medication (approx. 25 applications) with special rectal applicator and patient instructions.

Reed & Carnrick/Kenilworth, N.J. 07033



situation:
Post-operative . . . recent surgery . . . still confined to bed . . . or restricted ambulation . . .

constipation:
Constipating analgesics and sedatives . . . immobilization . . . reduced food and fluid intake . . . constipation common . . . fecal impaction a threat to be avoided . . .

laxation:
Gentle and predictable with colon-specific SENOKOT Tablets/ Granules. Virtually free from side effects in appropriate dosage.

Supplied: SENOKOT Tablets (small, easy-to-swallow)—Bottles of 50 and 100. SENOKOT Granules (delicious, cocoa-flavored)—4, 8 and 16 ounce (1 lb.) canisters.

Senokot
(standardized senna concentrate)
Tablets/Granules

a natural laxative

Purdue Frederick

© COPYRIGHT 1973, THE PURDUE FREDERICK COMPANY
NORWALK, CONN. 06856 A7033 128773

Annals of Surgery

A Monthly Review of Surgical Science and Practice

Also the official publication of
THE AMERICAN SURGICAL ASSOCIATION
THE SOUTHERN SURGICAL ASSOCIATION
PHILADELPHIA ACADEMY OF SURGERY
NEW YORK SURGICAL SOCIETY

EDITORIAL AND ADVISORY BOARD

JONATHAN E. RHOADS, M.D., *Chairman*
Philadelphia, Pa.

FRANK F. ALLBRITTEN, JR., M.D.
Kansas City, Kan.

WILLIAM A. ALTEMEIER, M.D.
Cincinnati, O.

W. GERALD AUSTEN, M.D.
Boston, Mass.

HENRY T. BAHNSON, M.D.
Pittsburgh, Pa.

BRIAN B. BLADES, M.D.
Washington, D. C.

WARREN H. COLE, M.D.
Asheville, N. C.

MICHAEL E. DE BAKEY, M.D.
Houston, Tex.

J. ENGLEBERT DUNPHY, M.D.
San Francisco, Calif.

FRANK L. A. GERBODE, M.D.
San Francisco, Calif.

FRANK GLENN, M.D.
New York, N. Y.

FRASER N. GURD, M.D.
Ottawa, Can.

JOHN W. KIRKLIN, M.D.
Birmingham, Ala.

WILLIAM P. LONGMIRE, JR., M.D.
Los Angeles, Calif.

LEONARD D. MILLER, M.D.
Philadelphia, Pa.

FRANCIS D. MOORE, M.D.
Boston, Mass.

JOHN H. MULHOLLAND, M.D.
New York, N. Y.

WILLIAM H. MULLER, JR., M.D.
Charlottesville, Va.

JOHN S. NAJARIAN, M.D.
Minneapolis, Minn.

WILLIAM F. RIENHOFF, JR., M.D.
Baltimore, Md.

PAUL S. RUSSELL, M.D.
Boston, Mass.

DAVID C. SABISTON, JR., M.D.
Durham, N. C.

JOHN A. SCHILLING, M.D.
Oklahoma City, Okla.

G. THOMAS SHIRES, M.D.
Dallas, Tex.

HARRIS B. SHUMACKER, JR., M.D.
Indianapolis, Ind.

FRANK C. SPENCER, M.D.
New York, N. Y.

JOHN D. STEWART, M.D.
Buffalo, N. Y.

NATHAN A. WOMACK, M.D.
Chapel Hill, N. C.

LIBRARY

J. B. LIPPINCOTT COMPANY, *Publishers*
Philadelphia and Toronto

Second-class postage paid at Philadelphia, Pa., and at additional mailing offices

© Copyright 1973, J. B. Lippincott Company, East Washington Square, Phila., Pa. 19105, Printed in U.S.A.

ANNALS OF SURGERY

Vol. 178 JULY 1973 No. 1

CONTENTS

1 Management of Acute Stress Ulcer after Cardiac Surgery, *Paul C. Taylor*, M.D., *Floyd D. Loop*, M.D., *Robert E. Hermann*, M.D., Cleveland, Ohio

6 Traumatic Rupture of the Aorta, *Panagiotis N. Symbas*, M.D., *Denis H. Tyras*, M.D., *R. Edwin Ware*, M.D., *David A. Diorio*, M.D., Atlanta, Georgia

13 Omental, Mesenteric, and Retroperitoneal Cysts: A Clinical Study of 33 New Cases, *Allan R. Walker*, M.D., *Thomas C. Putnam*, M.D., Rochester, New York

20 Delayed Cutaneous Hypersensitivity Reactions to Extracts of Malignant and Normal Human Breast Cells, *Crandall Alford, Ariel C. Hollinshead, Ronald B. Herberman*, Washington, D.C.

25 Axillary Metastases from Unknown Primary Sites, *Edward M. Copeland*, M.D., *Charles M. McBride*, M.D., Houston, Texas

28 Hartmann Procedure for Carcinoma of the Sigmoid and Rectum, *Robert D. Gongaware*, M.D., *Charles A. Slanetz, Jr.*, M.D., New York City

31 Leiomyoma of Meckel's Diverticulum—Preoperative Radiologic Demonstration: Case Report, *Imad F. Tabry*, M.D., *Victor H. Nassar*, M.D., *Jirayr P. Balikian*, M.D., Beirut, Lebanon

34 Perforation of the Small Intestine Secondary to Laparoscopic Tubal Cauterization, *Edward C. Saltzstein*, M.D., *Saul F. Schwartz*, M.D., *Carl J. Levinson*, M.D., Milwaukee, Wisconsin

37 Evaluation of a New Peritoneoscope As a Diagnostic Aid to the Surgeon, *George Berci*, M.D., *J. Manny Shore*, M.D., *Joel Panish*, M.D., *Leon Morgenstern*, M.D., Los Angeles, California

45 Non-Surgical Management of Cystic Hydatid Disease in Alaska: A Review of 30 Cases of *Echinococcus Granulosus* Infection Treated without Operation, *L. W. Pinch*, M.D., *J. F. Wilson*, M.D., Anchorage, Alaska

49 First Rib Resection in the Treatment of Thoracic Outlet Syndrome: Transaxillary and Posterior Thoracoplasty Approaches, *D. K. Roeder*, CDR MC USN, *M. Mills*, CAPT MC USN, *J. J. McHale*, CAPT MC USN, *B. M. Shepard*, CDR MC USN, *H. E. Ashworth*, CDR MC USN, Bethesda, Maryland

53 Icteric Thoracic Duct Lymph: Significance in Patients with Manifestations of Obstructive Jaundice, *Allan E. Dumont*, M.D., New York City

Dx: Duodenal ulcer...
Rx: Maalox®

Why do people develop duodenal ulcers?

No one knows with certainty . . . yet. Competitiveness? Perhaps. Stress? Aggressiveness? All probably play their parts.

But one thing *is* certain: in a disease characterized by a gastric-acid output that may be four times normal, antacid therapy is a vital adjunct to effective clinical management.

That's where Maalox comes in. It's America's number one antacid. And has been for years. The reasons?

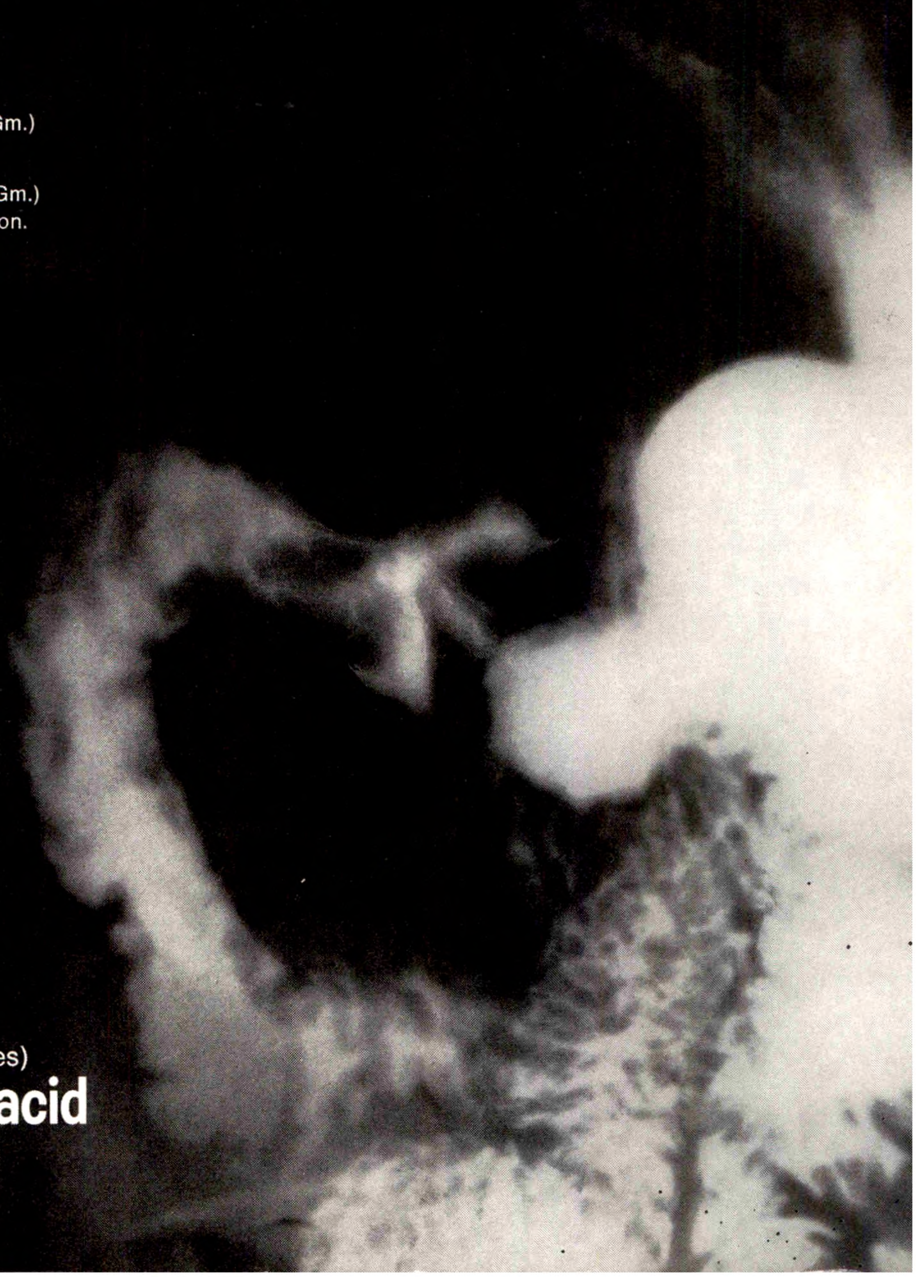
Maalox does precisely what an antacid, ideally, is intended to do. It works fast. It neutralizes effectively. It doesn't constipate. And its pleasant taste is well tolerated—definitely a major consideration in long-term therapy.

In any ulcer regimen, as you know, there are many factors to consider. But the inclusion of Maalox, as the antacid of choice, gives you and your patient one less thing to worry about.

Maalox® Suspension
(12 fl. oz. and 5 fl. oz. [plastic bottle]).

Maalox® No. 1 Tablets (0.4 Gm.)
—no sugar and low in sodium.

Maalox® No. 2 Tablets (0.8 Gm.)
—the "chew" tablet with double antacid action.



Maalox®
(a balanced combination of
magnesium and aluminum hydroxides)
the number one antacid

WILLIAM H. RORER, INC.
Fort Washington, Pa. 19034

CONTENTS *Continued*

59 Humoral Recognition Deficiency in the Etiology of Reticuloendothelial Depression Induced by Surgery, *William A. Scovill,* M.D., *Thomas M. Saba,* PH.D., Chicago, Illinois

65 Clinical Comparison of the End-to-Side and Side-to-Side Portacaval Shunt: Ten Year Follow-up, *Shunzaburo Iwatsuki,* M.D., *William P. Mikkelsen,* M.D., *Allan G. Redeker,* M.D., *Telfer B. Reynolds,* M.D., *Fred L. Turrill,* M.D., Los Angeles, California

70 Selection of Patients with Portal Hypertension for Splenorenal Shunt, *David P. Campbell,* M.D., *Constantine E. Anagnostopoulos,* M.D., *William W. L. Glenn,* M.D., New Haven, Connecticut

75 Early Respiratory Insufficiency in Acute Pancreatitis, *John H. C. Ranson,* B.M., B.CH., *Daniel F. Roses,* M.D., *Simon D. Fink,* M.D., New York City

80 Lesions of the Subclavian Artery: Survey of 31 Cases with Emphasis on Steal Syndromes, *Martin H. McMullan,* M.D., *James D. Hardy,* M.D., Jackson, Mississippi

87 Physiological Hemodilution: Interrelationships Between Hemodynamics and Blood Volume after Acute Blood Loss, *Joseph S. Carey,* M.D., Los Angeles, California

95 Cerebral Metabolism and Blood Flow after Circulatory Arrest During Deep Hypothermia, *Avio M. Perna,* M.D., *Timothy J. Gardner,* M.D., *Kamran Tabaddor,* M.D., *Robert K. Brawley,* M.D., *Vincent L. Gott,* M.D., Baltimore, Maryland

102 Plasma Catecholamines in Patients with Serious Postoperative Infection, *Alan C. Groves,* M.D., *John Griffiths,* M.D., *F. Leung,* PH.D., *R. N. Meek,* M.D., Ontario, Canada

108 Dipyridamole and Aspirin Tested Against an Experimental Model of Arterial Thrombosis, *J. E. Mayer, Jr., G. L. Hammond,* M.D., New Haven, Connecticut

113 Editorial: Thoughts Prompted by the Centennial of the American Public Health Association, *Allan E. Dumont,* M.D., New York City

115 Letter to the Editor

When Pain Cries for Relief!

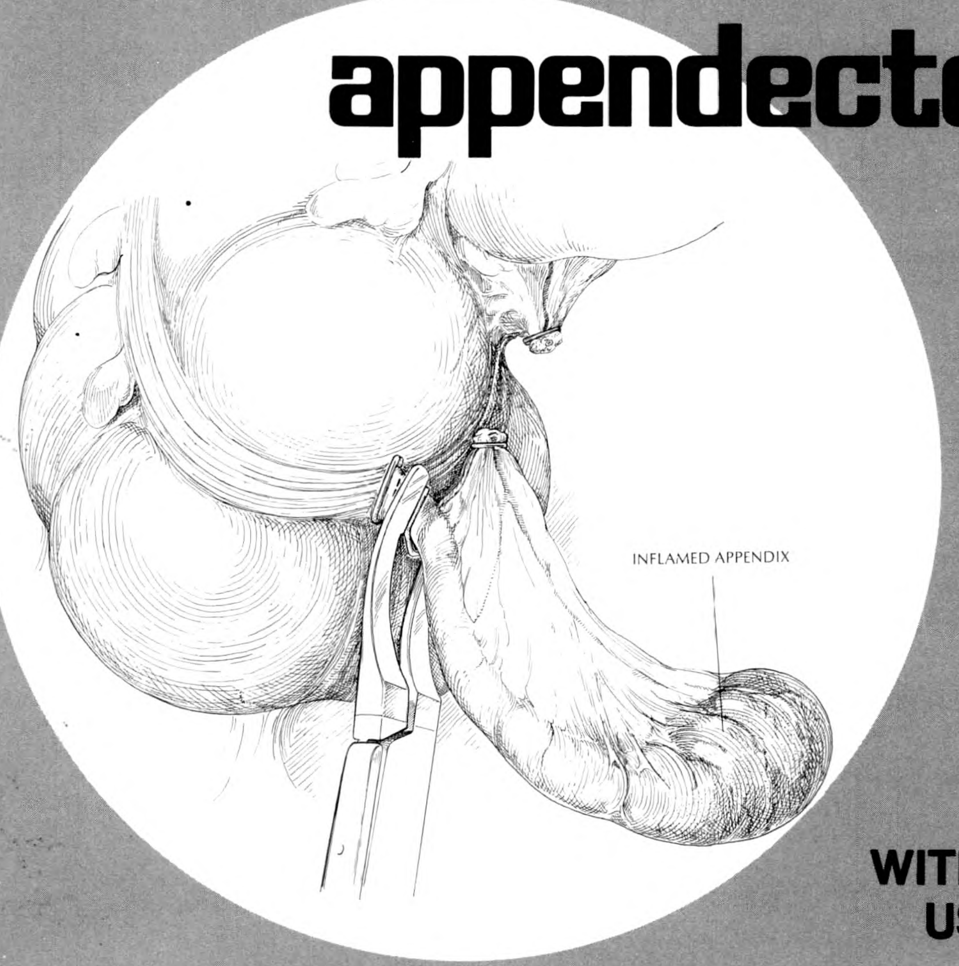
Start oral DILAUDID (hydromorphone) 2 to 4 mg. every four hours . . . to alleviate moderate to severe pain . . . well tolerated . . . minimal sedation

CONTRAINDICATIONS: Intracranial lesions associated with increased intracranial pressure, status asthmaticus. WARNINGS: May be habit forming. If given intravenously, injection should be given very slowly. PRECAUTIONS: Usual precautions for administration of opiate analgesics should be observed; the possibility of respiratory depression should be kept in mind. If significant respiratory depression should occur, it may be antagonized by the use of nalorphine hydrochloride or levallorphan tartrate. ADVERSE REACTIONS: Nausea, vomiting, dizziness, somnolence, anorexia and constipation may occur. Rapid intravenous injection increases the possibility of hypotension and respiratory depression. HOW SUPPLIED: Tablets — 1 mg., 2 mg., 3 mg., 4 mg. Rectal Suppositories — 3 mg. in cocoa butter base. Ampules — 1 ml., 1 mg., 2 mg., 3 mg., and 4 mg. per ml. with 0.2% sodium citrate, 0.2% citric acid solution. Cough Syrup — 1 mg. Dilaudid hydrochloride and 100 mg. glyceryl guaiacolate per 5 ml.

A Schedule II (CII) narcotic. Requires Federal BND order form.

Dilaudid®
(hydromorphone)

KNOLL PHARMACEUTICAL COMPANY · WHIPPANY, NEW JERSEY 07981
· TORONTO, CANADA



appendectomy

WITH THE USE OF

HEMOCLIPS®

SURGICAL OCCLUDING DEVICES

- **Saves operating time**
- **Greatly reduces trauma**
- **Large and medium size clips are grooved for positive, permanent, non-slip grip on tissue.**

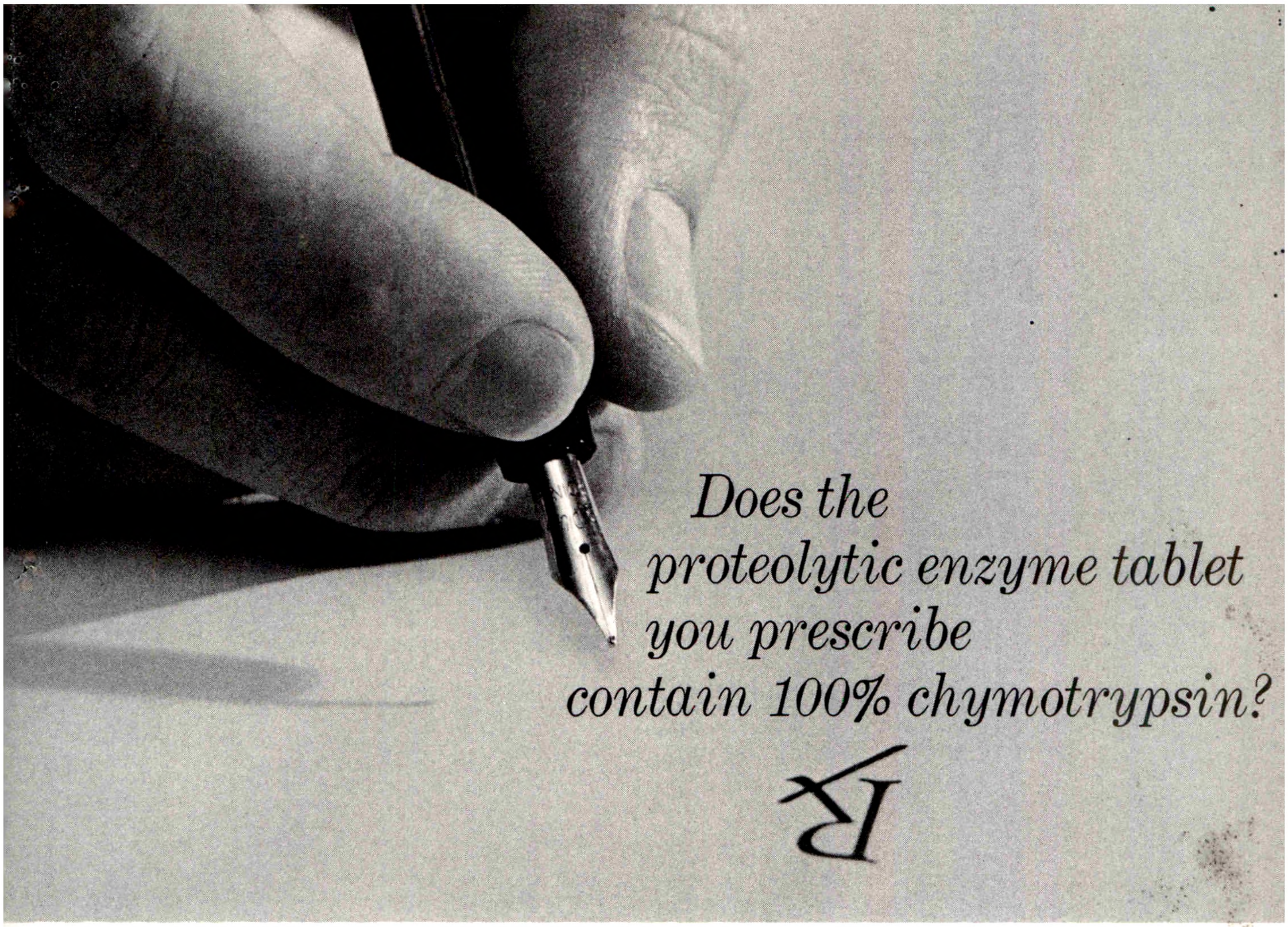
Peritonealization is accomplished with sutures in completing this procedure . . . one of many in which surgeons are finding the Hemoclip system highly effective.

Please contact Department 003 **for more detailed information.**

TM

WECK

EDWARD WECK & COMPANY, INC. • 49-33 31st Place, Long Island City, N.Y.11101



Only if it's Avazyme® or Avazyme®-100! And it can make a difference

After 30 minutes in human intestinal juice "63% of chymotryspin was still enzymatically active, whereas only 8% of the original trypsin activity could be detected."[1]

So if you're not getting the results you want from oral proteolytic enzymes, try the only all-chymotrypsin tablet. AVAZYME® (crystalline chymotrypsin–20 mg.) and double-strength AVAZYME®-100 (crystalline chymotrypsin – 40 mg.).

---

1. Wohlman, A. et al: Proc. Soc. Exp. Biol. & Med., 109: 26, 1962.

AVAZYME®: Each yellow tablet contains 20 mg. of crystalline chymotrypsin equivalent in proteolytic activity to 50,000 Wampole units (20,000 N.F. Units). The tablets have a special enteric coat to insure release in the intestine.

INDICATIONS

- Based on a review of this drug by the National Academy of Sciences — National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Relief of symptoms related to episiotomy.

Lack of substantial evidence of effectiveness: Adjunctive therapy for the resolution of inflammation and edema resulting from serious accidental trauma or surgical trauma.

Final classification of the less-than-effective indications requires further investigation.

ACTION: The experimental evidence for the anti-inflammatory action of chymotrypsin and other orally administered anti-inflammatory enzymes is based on animal studies.

CONTRAINDICATIONS: This drug is contraindicated in patients with a history of a prior allergic reaction to chymotrypsin.

WARNING: USE IN PREGNANCY — Safe use of this drug during pregnancy has not been established.

ADVERSE REACTIONS: An occasional patient may experience nausea, vomiting, diarrhea, and skin rash.

DOSAGE AND ADMINISTRATION: In mild conditions, one tablet four times daily. For more severe conditions, two tablets four times daily. There are no known incompatibilities.

DISCUSSION OF CLINICAL USE: Controlled clinical studies have demonstrated the anti-inflammatory action of Avazyme (Crystalline Chymotrypsin) in cases of urologic surgery, episiotomy, and surgery of the head and neck. Corroborative evidence in support of the clinical efficacy has been obtained upon treatment of inflammatory conditions resulting from surgical and accidental trauma.

ALSO AVAILABLE: AVAZYME®-100. White tablets containing crystalline chymotrypsin equivalent in proteolytic activity to 100,000 Wampole Units (approximately 40 mg.).

WAMPOLE LABORATORIES, Div. Denver Chemical Mfg. Co., Stamford, Ct. 06904 • In Canada: Denver Laboratories (Canada) Ltd., Toronto

AV100 AD-2

2/73

Kētalar®
(Ketamine HCl)
Progress Report

One year of nationwide clinical use; one decade of research and development at Parke-Davis. A continuing program that has made KETALAR anesthesia a reality.

In high-risk surgery, an added measure of safety

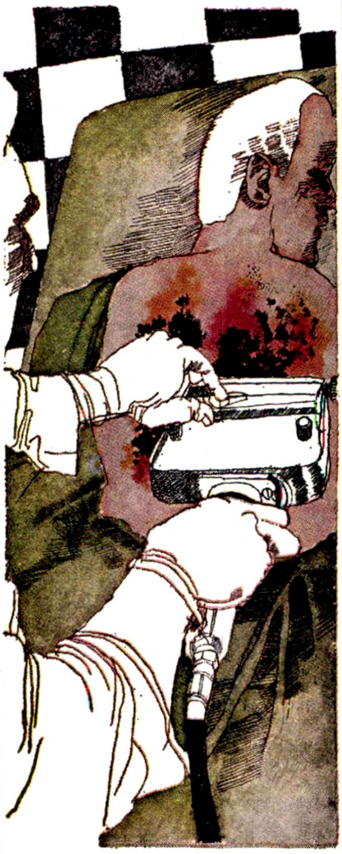
KETALAR *lessens* surgical risk for many emergency and "poor-risk" patients. It often elevates blood pressure. It usually affects respiration minimally and leaves protective laryngeal-pharyngeal reflexes intact. Airway patency can usually be maintained without **intubation.**

In routine induction, a smooth, uncomplicated start

KETALAR provides efficient induction for practically any anesthetic regimen *and* is administered I.M. or I.V. which greatly simplifies the procedure for children and adults alike. KETALAR is also clinically compatible with commonly used general anesthetics, pre- and postanesthetic medications, including anticholinergics, muscle relaxants, and tranquilizers.

In short procedures, more problems solved, fewer created

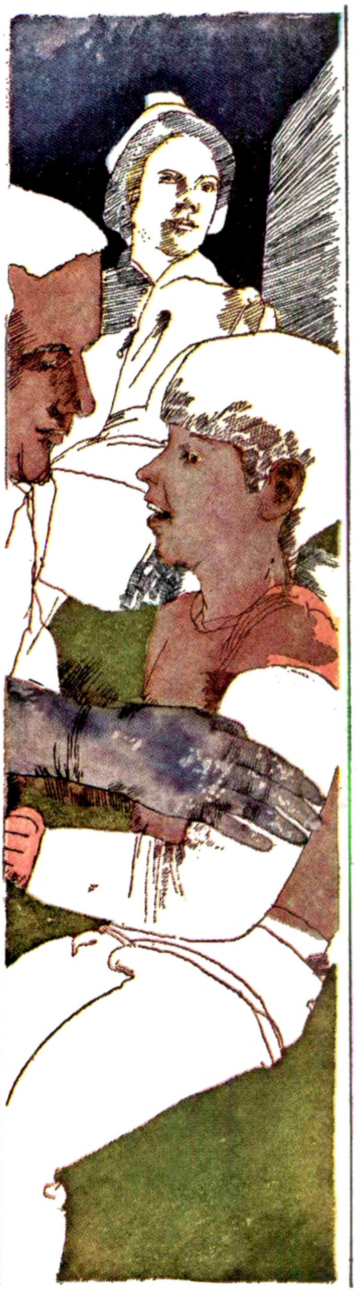
KETALAR, as sole agent, simplifies and improves anesthesia in a host of "problem procedures." It has proven to be especially valuable in the management of severe burn patients, and its rapid and profound analgesic effect provides a major advantage in numerous painful diagnostic tests and short surgical procedures not requiring skeletal muscle relaxation. The virtual absence of tachyphylaxis and organ/tissue accumulation is a definite plus in repetitive procedures. Growing experience with KETALAR shows that emergence reactions can be effectively reduced by allowing patients to awaken naturally with minimal verbal or tactile stimulation, and, where indicated, by employing agents such as droperidol or diazepam.



In pediatrics, a new era in anesthesia

KETALAR anesthesia represents a milestone in the management of infants and children. It offers—for the first time—efficient general anesthesia by *intramuscular* injection. In terms of both efficacy and convenience, the clinical experience with KETALAR may qualify it in many instances as the agent of choice for pediatric anesthesia.

KETALAR UPDATE:
Now indicated for use in cardiac catheterization.
Now available in new 100 mg./ml., 5 ml. vials for IM use.



See next page for prescribing information.

advancement in anesthesiology

Kētalar®
(Ketamine HCl)
Parke-Davis

advancement in anesthesiology

Ketalar®
(Ketamine HCl)
Parke-Davis

KETALAR (Ketamine Hydrochloride)

SPECIAL NOTE: EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12 PER CENT OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT DREAM-LIKE STATES, VIVID IMAGERY, HALLUCINATIONS AND EMERGENCE DELIRIUM. IN SOME CASES THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY LASTS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR. THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY.

THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS. IN ADDITION, THE USE OF A SMALL HYPNOTIC-DOSE OF A SHORT-ACTING OR ULTRASHORT-ACTING BARBITURATE OR OTHER AGENT SUCH AS DIAZEPAM MAY BE REQUIRED TO TERMINATE A SEVERE EMERGENCE REACTION. CERTAIN DRUGS SUCH AS DROPERIDOL OR DIAZEPAM INTRAMUSCULARLY HAVE ALSO BEEN USED IN AN ATTEMPT TO REDUCE THE INCIDENCE OF EMERGENCE REACTIONS: SUFFICIENT DATA HAVE NOT YET BEEN ACCUMULATED TO CONSTITUTE THOROUGH DOCUMENTATION. THE INCIDENCE OF EMERGENCE REACTIONS IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

INDICATIONS: Ketalar is recommended: 1. as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketalar is best suited for short procedures but it can be used, with additional doses, for longer procedures. 2. for the induction of anesthesia prior to the administration of other general anesthetic agents. 3. to supplement low-potency agents, such as nitrous oxide.

See package insert for full prescribing information.

CONTRAINDICATIONS: Ketalar is contraindicated in persons in whom a significant elevation of blood pressure would constitute a serious hazard and those who have shown hypersensitivity to the drug.

WARNINGS: Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation. Barbiturates and Ketalar *should not* be injected from the same syringe. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar. Postoperative confusional states may occur during the recovery period. Respiratory depression may occur with over-dosage or too rapid a rate of administration of Ketalar in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

USAGE IN PREGNANCY: Since the safe use in pregnancy, including obstetrics, has not been established, such use is not recommended.

PRECAUTIONS: Because pharyngeal and laryngeal reflexes are usually active, Ketalar should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances. Resuscitative equipment should be ready for use. *The incidence of emergence reactions may be reduced* if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note). The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response. In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

ADVERSE REACTIONS: *Cardiovascular:* Blood pressure and pulse rate are frequently elevated following administration of Ketalar. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketalar. Laryngospasms and other forms of airway obstruction have occurred during Ketalar anesthesia.

Eye: Diplopia and nystagmus have been noted following Ketalar administration. It also may cause a slight elevation in intraocular pressure measurement.

Psychological: (See Special Note).

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures.

Gastrointestinal: Anorexia, nausea or vomiting have been observed; however this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness.

General: Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

HOW SUPPLIED: Ketalar solutions containing the hydrochloride in concentrations equivalent to ketamine base are available in 5, 10, 20, and 50 ml. vials. These vials contain 100, 50, 10, and 10 mg./ml., respectively. Each vial is supplied individually and in cartons of 10.

LG

PARKE-DAVIS

108271R PA-631 *PARKE, DAVIS & COMPANY Detroit, Michigan 48232*

All of these mammals, except one, can synthesize vitamin C.

Man cannot.

Homo sapiens can neither synthesize vitamin C nor store most of the water soluble vitamins. They should be replenished every day.

Normally, man accomplishes this in his daily diet. But under conditions of illness, stress, in convalescence or following surgery, vitamin stores may be depleted or metabolic demands increased.

In such cases, Surbex-T may be indicated. Each tablet provides 500 mg. of vitamin C plus high potency B-complex.

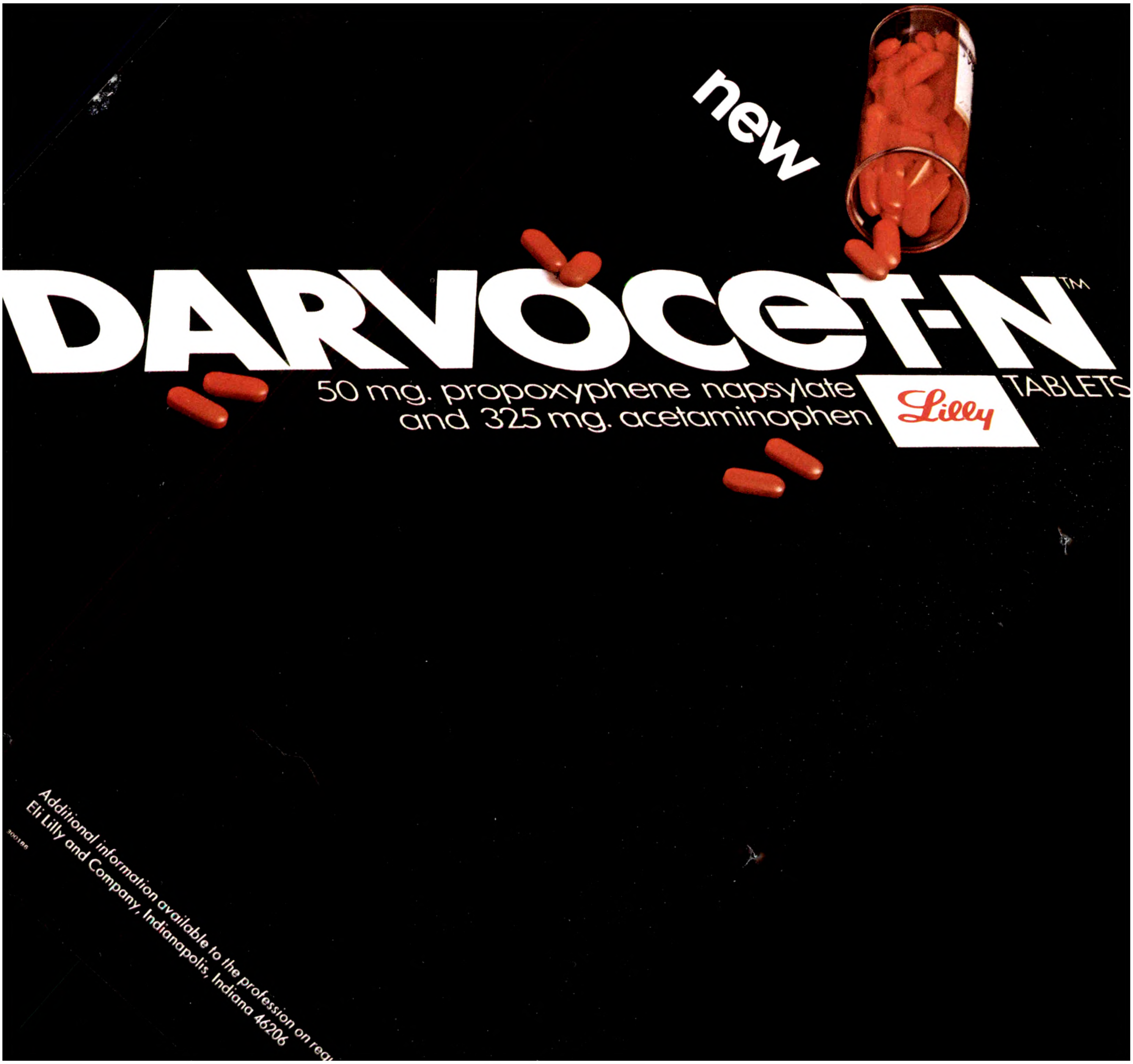
Where nutritional status must be preserved, Surbex-T can help restore what the body can *not* store.

306399R

SURBEX-T® 500 mg. of Vitamin C with High Potency B-Complex

Restores what the body cannot effectively store

ABBOTT



new

DARVOCET-N™
TABLETS

50 mg. propoxyphene napsylate
and 325 mg. acetaminophen

Lilly

Additional information available to the profession on req
Eli Lilly and Company, Indianapolis, Indiana 46206

300186

ANNALS OF SURGERY
Vol. 178 July 1973 No. 1

Management of Acute Stress Ulcer after Cardiac Surgery

PAUL C. TAYLOR, M.D., FLOYD D. LOOP, M.D.,
ROBERT E. HERMANN, M.D., F.A.C.S.

From the Department of Thoracic and Cardiovascular Surgery and the Department of General Surgery, The Cleveland Clinic Foundation and The Cleveland Clinic Educational Foundation, Cleveland, Ohio

ACUTE STRESS ULCERATION of the stomach and duodenum is being reported with increasing frequency after severe injuries, major burns, prolonged hypotension, during episodes of sepsis, while on steroid therapy, and after surgical procedures on the brain, major arteries and the heart. Frequently, massive hemorrhage from single or multiple stress ulcers occurs in patients who are in the early recovery period after major surgical procedures or who have been weakened by complications such as sepsis, cardiorespiratory insufficiency, renal failure, or cerebrovascular accident. The resultant mortality and morbidity from an additional surgical procedure in patients with stress ulcers have been high, ranging from 40% to 60% or higher in many reported series.[1-3,6,7] At present there is no standard or uniformly effective approach to this serious complication, partly because the underlying pathophysiology has not been clearly defined.

At the Cleveland Clinic, we have had a large experience with stress ulceration which occurred after cardiac surgery. We believe early surgical intervention is indicated in cases of hemorrhage unresponsive to intensive medical therapy. Since the stress-provoking situation may be only temporary, and because these patients often have a weakened physiologic reserve, we believe that conservative operations, whenever possible, may be the definitive surgical treatment.

Clinical Material

From 1964 through 1970 more than 5000 cardiac surgical procedures were performed at the Cleveland Clinic Hospital. This particular group of patients was selected for study because they represent an homogeneous type of stress and were subject to common stress factors during the early recovery period. Acute stress ulceration of the stomach or duodenum developed in 38 patients during the early postoperative period; 26 required emergency surgical intervention, and 12 patients were given intensive medical treatment only. Patients who had a history of peptic ulcer disease were not excluded from this study. The patients were from 14 to 65 years old (average 53 years). There were 29 men and 9 women (Table 1).

Previous Ulcer History. Twelve of the 38 patients had a definite history of previous peptic ulcer disease. In most patients, however, the symptoms had subsided years before cardiac surgery. Table 1 summarizes the above data with the 38 patients classified into medical and surgical groups.

Cardiac Diagnosis and Operation. In 28 patients (73.6%) myocardial revascularization procedures for coronary artery disease were performed. Nine patients (23.6%) had open-heart surgery for valvular disease, and one patient underwent correction for tetralogy of Fallot. Twenty-two (57.9%) of the cardiac procedures required extracorporeal circulation during the operation (Table 1). Table 2 lists the specific cardiac operations performed.

Submitted for publication June 16, 1972.

LIBRARY

TABLE 1. *Stress Ulcer in 38 Patients after Cardiac Surgery—Comparison of Medical and Surgical Groups*

	Surgical Treatment, 26 Patients	Medical Treatment, 12 Patients	Total Group %
Average Age	52	53	
Sex			
Men	19	10	76.3
Women	7	2	23.7
Previous Ulcer History	6	6	31.5
Cardiac Diagnosis			
Coronary artery disease	18	10	73.6
Valvular heart disease	7	2	23.6
Congenital heart disease	1	0	2.8
Pump Cases	16	6	57.9

Stress Factors

Psychological Stress. Patients undergoing cardiac surgery are subject to considerable emotional stress. Although mortality rates are low, particularly with myocardial revascularization procedures, many patients fear that they may not survive the operation. The added stress of modern postoperative intensive care units, with the almost constant stress-provoking activity and the temporary dissociation from normal day and night sequences, serve to compound the emotional stress experienced by each patient.

Physiological Stress. Although open-heart surgical procedures have been greatly simplified and operative time significantly shortened, the necessity of extracorporeal circulation, the operative manipulation of the heart or its arteries, and the occasional need for large quantities of transfused blood place a definite physiological stress on each patient.

Postoperative Complications. Other stress factors identified in the 38 patients in whom stress ulcers developed are summarized in Table 3. Postoperative myocardial infarction (diagnosed by electrocardiographic findings and elevated cardiac enzymes) developed in eight patients; in most instances, they did not have significant episodes of hypotension. Seven patients required reoperation, six for continued bleeding from within the chest during the early hours after cardiac surgery and one patient because of the development of a septic prosthetic valve with secondary periprosthetic leak. Postoperative respiratory insufficiency and pneumonia developed in five patients, in four of whom tracheostomy and respiratory assist devices were required. Three patients were receiving heparin at the onset of bleeding, one patient because of thrombophlebitis and two patients because of peripheral arterial embolization (one patient required embolectomy). Thirteen of the 38 patients had an uncomplicated postoperative course until stress ulcers developed. Long-term use of steroid drugs could not be incriminated as contributing to the development of any stress ulcer in this group of patients.

TABLE 2. *Heart Operations—38 Patients*

	Number of Patients
Myocardial Revascularization	
Internal mammary artery implantation	15
Saphenous vein bypass	7
Direct coronary artery dilation	2
Ventricular aneurysmectomy	4
Surgery for Valvular Heart Disease	
Open mitral commissurotomy	1
Mitral valve replacement	3
Aortic valve replacement	2
Open mitral commissurotomy plus aortic valve replacement	1
Mitral valve replacement plus aortic valve replacement	2
Congenital Heart Disease	
Tetralogy of Fallot	1
Total	38

TABLE 3. *Stress Factors after Heart Operations*

Factors	Number of Patients
Postoperative myocardial infarction	8
Reoperation for bleeding	6
Respiratory insufficiency	5
Congestive heart failure	3
Arrhythmia with hypotension	2
Peripheral arterial embolization	2
Thrombophlebitis	1
Postoperative cerebrovascular accident	1
Sepsis and leaking valve prosthesis	1
None	13

Pathology

The variation in number, location, and severity of ulcers found at operation was impressive. In this group of patients, slightly more than a third of the patients had multiple ulcers, the majority occurring in the stomach (Table 4). Another third had single ulcers, usually in the duodenum. In two patients with single duodenal ulcers, perforation was found at operation. One of these ulcers had eroded into the gastroduodenal artery and operation was performed to control massive hemorrhage.

TABLE 4. *Stress Ulcers Found at Operation*

		Number of Patients
Multiple Ulcers		10
Gastric	8	
Duodenal	2	
Single Ulcers		8
Duodenal	7	
Gastric	1	
Erosive Gastroduodenitis		7
Erosive Jejunitis		1
Total		26

In the second case, there was no associated bleeding and exploratory laparotomy was undertaken because of an acute surgical abdomen with intraperitoneal air. Seven patients had diffuse erosive gastroduodenitis. One patient with sudden, massive bleeding had an erosive, ulcerative process in a 3-foot segment of jejunum. Careful inspection at operation did not reveal any erosions in the stomach or duodenum.

Medical and Surgical Treatment

Onset of Symptoms. In 16 patients, the onset of upper gastrointestinal bleeding occurred during the first 5 days after cardiac surgery. In 17 patients, bleeding began during the second postoperative week (6 to 10 days). In the remaining five patients, bleeding did not begin until after the 10th day (11 to 27 days), one patient had no signs of bleeding until the 27th postoperative day.

In 12 patients the bleeding was controlled by medical treatment; of these patients eight had melena alone, but four also had associated hematemesis. An average of four units of whole blood were required for the patients treated medically.

The gastrointestinal bleeding was more severe, with associated hematemesis and frequent bloody bowel movements, in the majority of the 26 patients who required operation. The average transfusion requirement prior to operation was six units of whole blood. Twenty-one of these 26 patients were operated on within 24 hours after the onset of bleeding or perforation. In five patients, the rate of bleeding was less rapid and initially appeared to respond to medical treatment. These patients required surgical intervention from 2 to 5 days after the onset of bleeding. It was interesting that complaints of epigastric pain or distress were almost nonexistent in the 38 patients.

Medical Treatment. When the diagnosis of stress ulcer was made, an intensive medical program in accordance with the severity of bleeding was begun. If, at the outset, the bleeding appeared to be moderately severe or massive, a large lumen nasogastric tube was used for iced saline lavage and the administration of antacid solutions. The tube also served as an important monitoring device to assess the degree of continuing hemorrhage and to prevent vomiting and aspiration. Unless contraindicated, all patients were given large doses of tranquilizers. Whenever possible, *fresh* whole blood was used for volume replacement. Vitamin K was frequently given parenterally, even though a coagulation defect was not suspected or demonstrated clinically. When the bleeding subsided the nasogastric tube was removed, and as soon as tolerated, a strict hourly antacid program consisting of interval feedings of a bland diet was begun.

Table 5. *Operations Performed in 26 Patients*

Operation	Number of Patients
Vagotomy and pyloroplasty plus oversewing ulcer	17
Vagotomy and pyloroplasty plus wedge gastrectomy	1
Vagotomy and pyloroplasty plus resection of jejunum	1
Vagotomy and gastric resection	4
Subtotal gastrectomy	3
Total	26

Surgical Treatment. When it became apparent that the patient was not responding to medical treatment and was continuing to bleed beyond a reasonable number of blood transfusions, immediate surgical intervention was undertaken. As a general rule, we have considered the replacement of six units of whole blood (roughly one-half body blood volume) given during a 24 to 48 hours period to be an indication for surgical intervention. In some patients severe hemorrhage required immediate operation; in other patients bleeding persisted for 48 hours before operation.

The specific operative procedures performed on the 26 patients who required surgical control of the ulcer diathesis are listed in Table 5. It is apparent that we have preferred truncal vagotomy and pyloroplasty with oversewing of the ulcer or limited resections as a faster and "lesser" surgical procedure in the majority of these patients (19 patients), although seven subtotal gastric resections were performed, four with vagotomy.

When possible, vagotomy was performed before the stomach was opened. A long gastrotomy incision was made (Fig. 1) for inspection of the entire gastric mucosa. When multiple bleeding ulcers were found, these were suture-ligated. After an adequate Kocher maneuver, a longitudinal incision was made across the pylorus to visualize the distal antrum, pyloric channel, and duodenum. Any bleeding ulcers were again suture-ligated and the pyloric incision was closed transversely in a Heineke-Mikulicz pyloroplasty with a single layer of interrupted silk sutures. The gastrotomy opening was closed in two layers. When the ulcerative process could not be controlled by vagotomy and pyloroplasty with suture-ligation of bleeding ulcerations or when the erosive process seemed unusually severe, a gastric resection was performed. Postoperatively, a sump type of nasogastric tube, connected to low Gomco suction or gravity drainage, was used with limited irrigation of the stomach to prevent further irritation and bleeding from the friable gastric mucosa.

Results

The overall mortality (30 days or in-hospital death) for these 38 patients after medical and surgical treatment

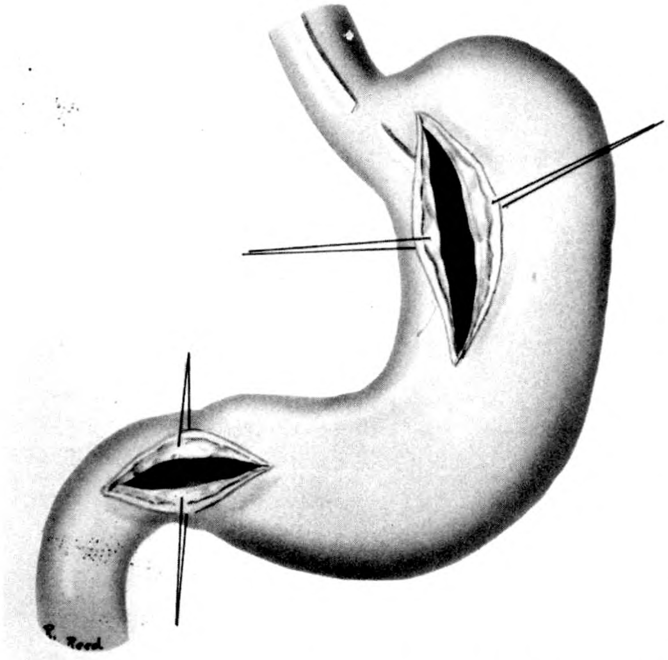


FIG. 1. Artist's drawing showing gastric and pyloric incisions following truncal vagotomy. It is important to inspect all of the gastroduodenal mucosa for discrete bleeding ulcers.

was 23.6% (Table 6). Only one patient, severely bleeding and comatose from a massive cerebrovascular accident, died during medical therapy. In the 11 other patients treated medically, the bleeding stopped promptly.

There were eight deaths after surgical treatment, an operative mortality of 30.7%; seven of these eight patients died from cardiovascular or pulmonary complications. Only one patient in the surgical group died from continuing or uncontrolled hemorrhage. This patient had a vagotomy and pyloroplasty followed by a 95% gastric resection; he continued to bleed and died of a pulmonary embolus.

Reoperation was necessary in two other patients; one patient required a gastric resection for a second, massive bleeding episode 1 week after vagotomy and pyloroplasty, and reoperation was performed in the other patient, who initially had gastric resection, because of leakage from the suture line of the anastomosis. The latter patient died of a myocardial infarction after the second procedure.

TABLE 6. *Mortality after Medical and Surgical Treatment of Acute Stress Ulcers in 38 Patients*

	Mortality, Patients	Per cent
Overall mortality	9/38	23.6
Medical treatment	1/12	8.3
Surgical treatment	8/26	30.7
Vagotomy and pyloroplasty	6/19	31.6
Gastric resection with or without vagotomy	2/7	28.6

Seven other patients had minor recurrent bleeding after surgical treatment (all had vagotomy and pyloroplasty) but none of these patients required reoperation. An average of two to three whole blood transfusions were given for these bleeding episodes.

The major cause of death in each of the eight patients who died after their gastric operation was cardiopulmonary insufficiency secondary to congestive heart failure, pneumonia, and sepsis. Recurrent gastrointestinal bleeding was a factor in only one of these patients. For the entire group of patients, mortality as a result of recurrent or uncontrolled bleeding was 5.3%; death resulted from cardiorespiratory complications in 18.4%.

Discussion

These cases represent a homogeneous group of patients with a true stress ulcer diathesis. All of the patients underwent major cardiac surgical procedures and a significant number had secondary complications prior to the onset of the stress ulcer syndrome. During the last 2 years, the morbidity and mortality of cardiac surgery has continued to decline. The incidence of stress ulcers has also markedly declined.

Whatever factors combine to cause stress ulceration of the stomach or duodenum, it is our distinct clinical impression that these factors are temporary. Prolonged hypotension, sepsis, and cardiac or pulmonary insufficiency contribute to the stress of any major surgical procedure. If such complications can be controlled or alleviated in a short period, mild or even moderate stress bleeding may be brought under control by medical means. Only emergency surgical intervention may save the patient if massive hemorrhage requiring rapid or major blood volume replacement develops.

In our experience with stress bleeding after cardiac surgery, we have found that vagotomy and pyloroplasty with oversewing of the bleeding ulcers stopped the bleeding and controlled the ulcer diathesis in the majority of patients. We have reserved vagotomy and gastric resection for those patients who continued to bleed after vagotomy and pyloroplasty or who had an unusually severe erosive process. This conservative approach has resulted in a lower mortality and morbidity than has been generally reported. We found that recurrent bleeding after a conservative operation was a problem in only two patients who required reoperation; in seven additional patients it was minor and ceased after a day or two. Only one of the 26 patients who underwent surgical treatment died as a result of continuing hemorrhage.

Many surgeons have advocated a subtotal, or total gastrectomy as the standard surgical approach to all stress ulcers.[1,5–7] We do not feel that this operative approach, with its potentially higher morbidity and mortality, is justified for all patients with stress ulcers, even though the present study does not document a higher mortality for gastric resection in this series. Vagotomy and gastric resection may be indicated as the primary operative procedure in patients who develop stress ulcers after a major burn or a severe injury, both of which represent a continuing stress.

We agree with Kirtley, Scott, Sawyers *et al.*,[4] that the etiology of stress ulcer remains unknown and that surgical treatment is empiric. Most studies have emphasized the role of vagotomy in decreasing blood flow to the gastric mucosa. On the basis of our clinical experience, we continue to advocate conservative ulcer operations, vagotomy and pyloroplasty with suture ligation of the ulcers or, when necessary, vagotomy and antrectomy in the treatment of stress ulcers.

Summary

In this report, 38 patients are discussed who developed stress ulcers after cardiac surgery. Twenty-six patients required surgical intervention for control of massive hemorrhage or perforation; in 12, the bleeding subsided with intensive medical treatment. Because we believe whatever factors combine to provoke the stress ulcer syndrome are generally temporary, we have favored the more conservative operative approach of vagotomy and pyloroplasty with oversewing of the bleeding ulcers as opposed to the more extensive procedure of gastric resection which may result in a higher morbidity and mortality. In this group of patients, the incidence of recurrent bleeding following vagotomy and pyloroplasty with oversewing of bleeding ulcers was not a significant problem.

References

1. Crawford, F. A., Hammon, J. W., Jr. and Shingleton, W. W.: The Stress Ulcer Syndrome; a Clinical and Pathologic Review. Am. J. Surg., **121**:644, 1971.
2. Douglass, H. O., Jr. and LeVeen, H. H.: Stress Ulcers; a Clinical and Experimental Study Showing the Roles of Mucosal Susceptibility and Hypersecretion. Arch. Surg., **100**: 178, 1970.
3. Goodman, A. A. and Frey, C. F.: Massive Upper Gastrointestinal Hemorrhage Following Surgical Operations. Ann. Surg., **167**:180, 1968.
4. Kirtley, J. A., Scott, H. W., Jr., Sawyers, J. L., Graves, H. A., Jr. and Lawler, M. R.: The Surgical Management of Stress Ulcers. Ann. Surg., **169**:801, 1969.
5. Lucas, C. E., Sugawa, C., Friend, W. and Walt, A. J.: Therapeutic Implications of Disturbed Gastric Physiology in Patients with Stress Ulcerations. Am. J. Surg., **123**:25, 1972.
6. Lulu, D. J. and Dragstedt, L. R., II: Massive Bleeding Due to Acute Hemorrhagic Gastritis. Arch. Surg., **101**:550, 1970.
7. Menguy, R., Gadacz, T. and Zajtchuk, R.: The Surgical Management of Acute Gastric Mucosal Bleeding. Arch. Surg., **99**:198, 1969.

Traumatic Rupture of the Aorta

PANAGIOTIS N. SYMBAS, M.D., DENIS H. TYRAS, M.D.,
R. EDWIN WARE, M.D., DAVID A. DIORIO, M.D.

*From the Joseph B. Whitehead Department of Surgery,
Division of Thoracic and Cardiovascular Surgery,
Emory University School of Medicine, Atlanta,
Georgia 30303, and Grady Memorial Hospital,
Atlanta, Georgia 30303*

HIGH SPEED automotive travel, having become available to millions of people during recent years, has resulted in an increasing incidence of injuries from blunt trauma.[19,20] One of the most lethal of all intrathoracic injuries caused by blunt trauma is rupture of the thoracic aorta.

The purpose of this communication is to describe six patients with rupture of the thoracic aorta from blunt trauma, one of whom has previously been reported,[35] treated in the immediate postinjury period during the last 4 years at Grady Memorial and Emory University Hospitals and to review the English literature on the early and delayed repair of this lesion.

Case Reports

Case 1. B. J. D., a 27-year-old woman, was injured in an automobile accident in June, 1968. Admission blood pressure in the right upper extremity was 120/70 mm. Hg. Pulse was 110/minute with diminished amplitude over the left radial artery, and respirations were labored at a rate of 26/minute. Subcutaneous emphysema was present over the anterior chestwall, which moved paradoxically with respiration. A chest roentgenogram revealed a right scapular fracture, bilateral pneumothorax, and widening of the superior mediastinum. Hematocrit was 42%. Bilateral tube thoracostomies and tracheostomy were performed and assisted ventilation was instituted.

Soon after admission, in addition to anterior chest pain, the patient complained of severe midscapular pain and coldness of the left arm. The blood pressure in the right arm had risen to 170/75 mm. Hg, no pulse could be palpated in the cold left arm, and the systolic blood pressure was 90 mm. Hg by palpation in the right leg. A repeat chest roentgenogram revealed progressive mediastinal widening and displacement of the trachea to the right. In addition, after a technically unsuccessful attempt of transbrachial aortography, a forward venous angiogram demonstrated a filling defect between the left common carotid and left subclavian arteries and lack of filling of the left subclavian artery. The patient was operated upon 5 hours after injury. Utilizing a left posterolateral incision, the chest was entered through the fourth intercostal space revealing 300 ml. of blood and a large hematoma over the aortic arch and isthmus. Femoral vein to femoral artery partial cardiopulmonary bypass was instituted, and the aorta was cross-clamped proximal and distal to the hematoma. Evacuation of the hematoma unveiled the suspected transections of the left subclavian artery at its origin and of the aortic arch just distal to the origin of the left common carotid artery. The anterior wall of the false aneurysm was resected, and the continuity of the aorta and left subclavian artery was restored with the use of woven Dacron grafts.

Postoperative course was relatively uncomplicated, and the patient was discharged 23 days after injury. On subsequent follow-up 3½ years after injury, the patient was asymptomatic with a normal chest roentgenogram, aortogram, and left subclavian arteriogram.

Case 2. W. W., a 23-year-old man, was involved in an automobile accident in July, 1969, striking his chest on the steering wheel. When brought to the emergency clinic one hour later, he complained of severe substernal chest pain. Blood pressure was 120/80 mm. Hg in the left arm, 115/75 mm. Hg in the right arm, and the pulse was 90/minute. Fractures of the mandible and of several teeth, a laceration of the lower lip, and minimal contusion of the anterior chest wall were noted, with no respiratory distress. The femoral and dorsalis pedis pulses were diminished bilaterally. Chest roentgenograms revealed a small left hemothorax and widening of the mediastinum, and the admission hematocrit was 48%. An emergency retrograde aortogram demonstrated an aneurysm of the aorta with two linear filling defects just distal to the left subclavian artery.

Thirteen hours after injury, the patient was operated upon. Through a left thoracotomy, evacuation of approximately 500 ml. of blood revealed a false aneurysm 4 cm. distal to the origin of the left subclavian artery. Under femoral vein to femoral artery partial cardiopulmonary bypass, the aneurysm was opened, revealing a 5 cm. separation between opposing edges of the transected aortic isthmus. The anterior wall of the false aneurysm was removed, and the continuity of the aorta was restored with

---

Submitted for publication March 15, 1972.

Supported in part by National Institute of Health Training Grant T 12 HE 05861.

Reprint requests to: Dr. P. N. Symbas, 69 Butler Street, S.E., Atlanta, Georgia.

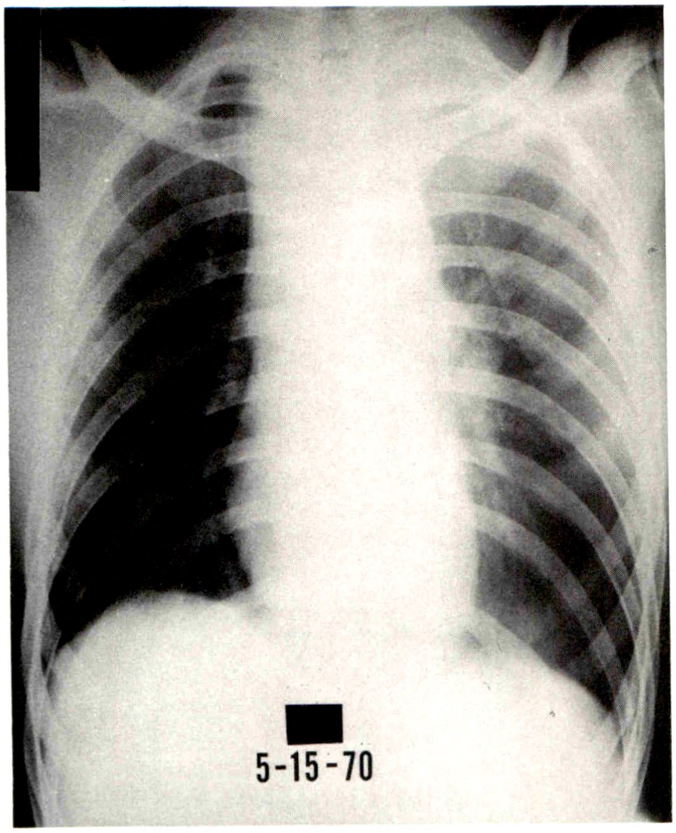


FIG. 1. Admission portable chest roentgenogram showing widening of the mediastinal shadow and left hemothorax.

a 22 mm. diameter woven dacron prosthesis. The postoperative course was uncomplicated, and the patient was discharged 10 days after operation. One year postoperatively he was asymptomatic, and chest roentgenogram was within normal limits.

Case 3. J. R. P., a 19-year-old man, was thrown from a motorcycle in July, 1969. He was taken to another hospital 10 minutes after the accident, at which time blood pressure was 100/68 mm. Hg. Injuries included a laceration of the right ankle and fractures of the right patella, left tibia and fibula. Serial chest roentgenograms over the next 5 hours demonstrated progressive widening of the mediastinum, elevation of the left hemidiaphragm, and tracheal deviation to the right. One liter of whole blood was given, and the patient was transferred to our hospital.

On admission, 7 hours after injury, the patient complained of anterior chest and upper abdominal pain. Pulse was 88/min., and blood pressure was 165/70 mm. Hg in the right arm, and 135/65 mm. Hg in the left arm. Femoral pulses were present but diminished bilaterally, and the hematocrit was 32%. A percutaneous transfemoral retrograde aortogram revealed an aneurysm of the aorta, distal to the left subclavian artery.

Eleven hours after injury, the patient was operated upon. Approximately 400 cc. of blood were evacuated from the left pleural space, revealing a large hematoma at the aortic isthmus. Under femoral vein to femoral artery partial bypass, a circumferential tear of the aortic intima and media with a 6 cm. separation just distal to the origin of the left subclavian artery was repaired with a woven Dacron graft. The patient was discharged 16 days after operation and was doing very well on follow-up 2 years postoperatively.

Case 4. J. A., a 19-year-old man, in June 1970, sustained multiple body contusions and abrasions in a motorcycle accident. On admission to the hospital 20 minutes after injury, he was restless, combative, and disoriented, but had no focal neurologic deficits. Blood pressure was 80/50 mm. Hg, pulse 120/minute, and the heart and lungs were normal on admission examination. The abdomen was tender and slightly distended, the left thigh was swollen and tender, and the urine was blood-tinged. Blood and blood volume expanders were infused with a slow rise of the arterial pressure to 180/90 mm. Hg. ECG, IVP, and cystogram were within normal limits, and a chest roentgenogram showed a left hemothorax and widening of the mediastinum (Fig. 1). A left thoracostomy tube was inserted, and 850 ml. of blood were evacuated over a 2 to 3-hour period with no further drainage thereafter. Other roentgenographic studies revealed fractures of the left temporal bone, left femur, pelvis, left tibia and fibula and left wrist bones.

On the day of admission, laparotomy was performed for persistent abdominal tenderness and distension, but no lesion was found. The postoperative course was satisfactory, with blood pressure in the upper extremities varying from 170/90 to 200/100 mm. Hg and all peripheral pulses remaining distinctly palpable and equal.

On the second hospital day, a chest roentgenogram showed clearing of the left hemothorax and no further widening of the mediastinum (Fig. 2). Repeat chest roentgenogram on the fourth day, however, demonstrated a right apical density which appeared to be a hemothorax although the vital signs and peripheral pulses remain unchanged (Fig. 3). This new development and the persistent upper extremity hypertension engendered a suspicion of rupture of the aorta, and a percutaneous right transaxillary

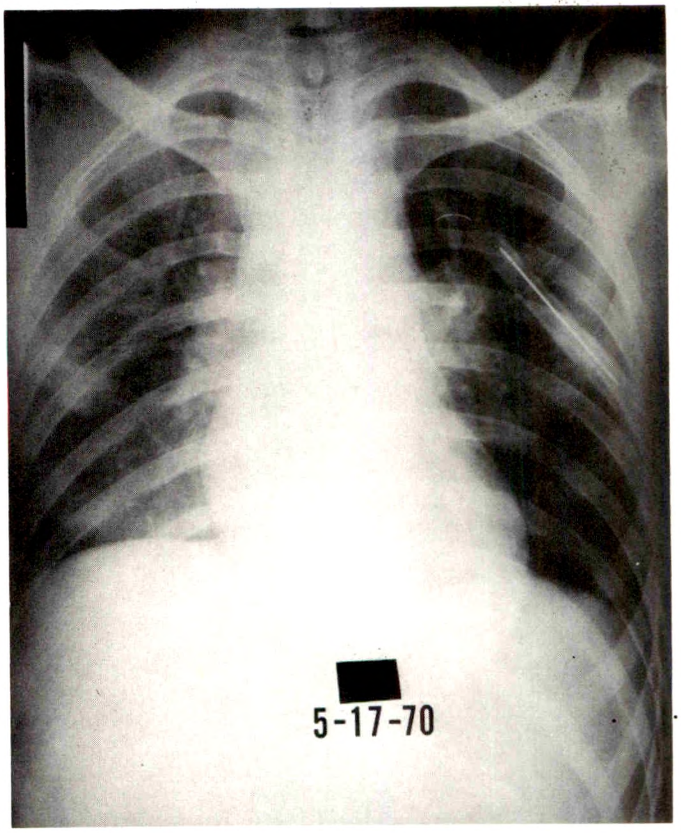


FIG. 2. Chest roentgenogram 2 days later showing no further widening of the mediastinal shadow.

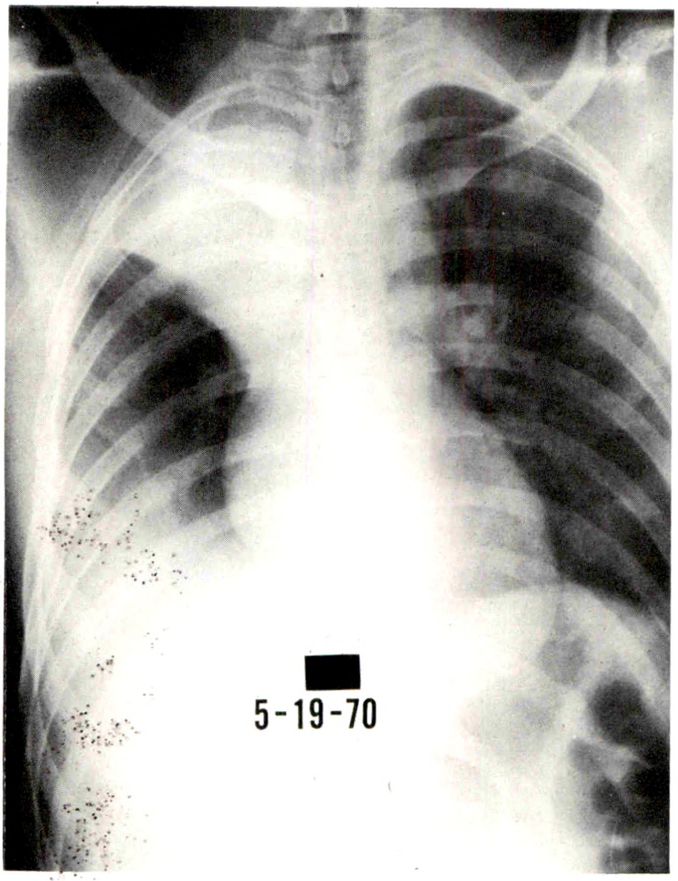


FIG. 3. Chest roentgenogram 4 days after admission demonstrating right apical density with no changes of the mediastinal shadow.

aortogram was performed. This demonstrated a 4 cm. by 6 cm. aneurysm of the aortic isthmus (Fig. 4), and one hour later the patient was operated upon. When the left pleural space was opened, a pulsatile dark red mass was exposed over the descending thoracic aorta, distal to the left subclavian artery. Femoral vein to femoral artery partial bypass was instituted and the pseudoaneurysm was opened, revealing a 6 cm. separation between the retracted ends of aortic intima and media. The anterior wall of the false aneurysm was resected, as was a ring of disrupted aortic wall at the proximal area of injury, and the continuity of the aorta was restored with the interposition of a woven Dacron graft.

The postoperative course was benign, and the patient was transferred to the orthopedic service 7 days after operation, where he underwent prolonged convalescence for the multiple fractures. Follow-up chest roentgenograms and blood pressures have been within normal limits.

Case 5. G. S., a 20-year-old man, fell from a height of approximately 50 feet and was admitted in December, 1971, with multiple fractures and paraplegia. Blood pressure was 90/60 mm. Hg, with a pulse rate of 108/minute, and the peripheral pulses were diminished in all extremities. Roentgenographic studies revealed multiple fractures of both forearms and wrists, the left lower leg, both feet, and compression fractures of L_4 and L_5. The admission chest roentgenogram demonstrated mediastinal widening and a left hemothorax. The multiple gross fractures and shock were felt to be the cause of the pulse deficit in all extremities, a condition which resolved with reduction of the fractures and institution of IV fluids. Paraplegia was felt to be the result of the L_4 and L_5 compression fractures. Insertion of a left thoracostomy tube resulted in drainage of approximately 1200 cc. of blood, two units of which were returned to the patient by autotransfusion. After initial recovery, the pulse amplitude and blood pressure in the extremities remained within normal limits, and no murmurs or bruits were present. However, the paraplegia persisted. Because of concern for persistent mediastinal widening on daily chest roentgenograms, on the seventh day of hospitalization aortography was performed, revealing a traumatic aneurysm of the aortic isthmus. At thoracotomy the following day, an 8 cm. separation between the ends of the ruptured aorta was restored with a Dacron graft under femoral vein to femoral artery bypass. The patient's postoperative course was satisfactory, and total recovery from cardiovascular injury was uneventful. On the second postoperative day, the patient appeared to be regaining sensation of the lower extremities, and on the fifth postoperative day, definite improvement in motor function was noted in the lower extremities. On the 13th postoperative day, the patient was transferred to a private hospital where continued improvement in his neurologic status was noted.

Case 6. M. A., a 54-year-old woman, was involved in an auto accident resulting in blunt chest trauma and a flail segment of the right anterolateral chest wall in January 1972. On arrival to the emergency clinic, blood pressure was 100/60 mm. Hg., pulse 132/minute, and respirations were labored. In addition to the paradoxical motion of the right chest wall, associated with decreased breath sounds bilaterally, significant physical findings included the absence of radial pulses with palpable carotid and femoral pulses, all without bruit or thrill. Admission chest roentgenograms demonstrated multiple rib fractures at the site of the flail segment, in addition to a left hemothorax and a markedly widened mediastinum.

Endotracheal intubation was accomplished for assisted ventilation, and bilateral tube thoracostomies were performed. During

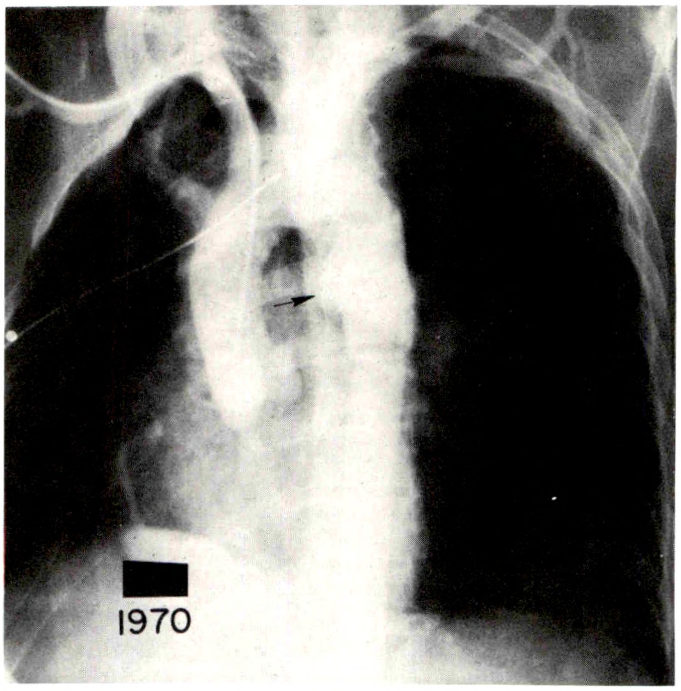


FIG. 4. Aortogram performed on the fourth day after admission showing an aneurysm at the aortic isthmus and an intraluminal linear filling defect.

TABLE 1. *Site of Aortic Rupture*

Site	Early	Chronic	Total
Ascending Aorta	3	2	5
Aortic Arch	1	2	3
Aortic Isthmus	82	114	196
Distal Descending Aorta	2	2	4
Unspecified	2		2

the latter procedure, the patient suffered a cardiac arrest, and, although vigorous attempts at resuscitation were instituted, effective cardiac action could not be re-established.

At autopsy, a deep laceration of the liver with significant hemoperitoneum, multiple rib fractures, left hemothorax, and transection of all the great arteries with rupture of the aortic isthmus were found.

Review of the Literature

In reviewing the English literature, we have found 204 case reports of surgical treatment of thoracic aortic rupture from blunt trauma. The overwhelming majority of the patients have been injured in vehicular accidents, either as a passenger (84%), or as a pedestrian (6%). The most common site of rupture was the aortic isthmus (Table 1), comprising 95% of all patients surgically treated. The symptoms and signs of the reported instances are illustrated in Table 2. In the patients treated during the acute period, the most common symptom was chest pain (26%), and the most prominent physical findings included differences in pulse amplitude (37%), acute onset of upper extremity hypertension (31%), and a systolic murmur (26%), frequently heard at the base of the heart or in the midscapular area. The commonest chest roentgenographic finding was mediastinal widening (87%) (Table 3). Coexistent organ injuries included rib, sternal, extremity, or pelvic fractures, and intra-abdominal injury (Table 4). More than sixty patients have had successful early repair, with approximately 50% accomplished within 55 minutes[12] to 24 hours after injury (Table 5). By far the most popular technic utilized in both early and late repair was partial cardiopulmonary bypass from the left atrium to the femoral artery (Table 6).

TABLE 2. *Symptoms and Signs of Aortic Rupture*

	Early	Chronic	Total
Chest pain	23	30	53
Dyspnea	9	17	26
Back pain	4	4	8
Hoarseness	1	10	11
Dysphagia	4	6	10
Cough	0	10	10
Pulse differences	31	10	41
Hypertension	26	6	32
Systolic murmur	22	22	44
Paraplegia	10	1	11
Vocal cord palsy	0	7	7

TABLE 3. *Roentgenographic Findings on Initial Admission*

	Early	Chronic	Total
Mediastinal widening	73	23	96
Hemothorax	36	16	52
Tracheal deviation	9	1	10
Esophageal narrowing	0	6	6

Discussion

The era of high speed transportation has brought with it a changing pattern of traumatic injuries. Rupture of the thoracic aorta, which is a distinct and not infrequent entity, is a striking example of this phenomenon. The incidence of this catastrophic clinical event became apparent with Strassman's report in 1947[34] and the monumental work of Parmley *et al.* in 1958.[28] The most frequent sites of rupture of the aorta are the ascending aorta, just proximal to the origin of the innominate artery, and the descending aorta, just distal to the origin of the left subclavian artery. Autopsy cases with *isolated* aortic rupture from nonpenetrating trauma have demonstrated that 50–60% occur just distal to the left subclavian artery, and 10–20% involve the ascending aorta,[19,20,34] whereas, of those associated with cardiac injury, 52% occur in the ascending aorta and only 32% in the region of the ligamentum arteriosum.[28] Because of the high mortality of patients with aortic rupture associated with cardiac injury, the overwhelming majority of patients surviving long enough for surgical treatment have manifested rupture at the aortic isthmus (Table 1).

The factors responsible for traumatic rupture of the aorta have been previously discussed in detail,[36] and, in general, can be summarized as follows: torsion stress and the stress from a "waterhammer effect" produced during blunt trauma appear to be predominantly responsible for rupture of the ascending aorta, whereas the shearing and bending stresses appear to injure the descending aorta. The torn intima and media of the distal aortic segment, acting as a "ball valve" flap and the mediastinal hematoma compressing the aortic isthmus produce the "acute coarctation syndrome"[25,26] of upper extremity hypertension, which has been found to be the most frequent manifestation of acute rupture of the

TABLE 4. *Injuries Associated with Aortic Rupture*

	Early	Chronic	Total
Rib fracture	29	32	61
Sternal fracture	3	3	6
Extremity fracture	24	22	46
Pelvic fracture	10	4	14
Intra-abdominal injury	16	5	21
Diaphragmatic rupture	10	0	10
Skull fracture	1	5	6

TABLE 5. *Time and Results of Surgical Treatment of Aortic Rupture*

	Time of Repair	Survived	Died
Early	< 24 hours	33	11
	1–2 days	13	4
	3–5 days	8	3
	6–7 days	3	0
	1–3 weeks	10	5
Late	3 weeks–1 year	26	8
	1–5 years	27	5
	6–10 years	17	3
	> 10 years	26	2
	Unspecified	5	1

aorta,[26,27] with paraplegia and transient anuria being rare sequelae of this injury (Table 2). A systolic murmur heard at the base of the heart or in the midcapular area was detected in 25% of the acute cases, whereas signs of encroachment upon neighboring structures, *e.g.*, vocal cord palsy[32] or tracheal[18] and superior vena caval compression,[10,33] are mainly manifestations of an expanding chronic aortic aneurysm.

The chest roentgenographic features of this injury have been well delineated in previous reports[14,16,17,24,31] and include widening of the superior mediastinum, tracheal displacement to the right, narrowing of the carinal angle, depression of the left mainstem bronchus, irregularity in the aortic knob contour, and partial obscuration of the aortic arch by mediastinal hematoma. Widening of the mediastinum alone has been the most common abnormality seen (Table 3).

Therefore, the triad of: difference in pulse amplitude between upper and lower extremities; hypertension of the upper extremities; and widening of the mediastinum has been the most constant finding in rupture of the aorta.

It must be remembered, however, that small mediastinal vessel injury may result in hematoma formation and mediastinal widening which usually regresses spontaneously over a period of several days on serial chest roentgenograms.[13,25,33] For this reason, widening of the mediastinum on the initial chest roentgenogram with no other signs of aortic rupture does not dictate immediate aortography, although this study is very desirable. Chest roentgenography should be repeated daily in these patients, and rupture of the aorta should be strongly suspected if progression or no regression of the mediastinal widening is seen.

TABLE 6. *Surgical Technics Used for the Repair of the Aortic Rupture*

	Early		Chronic	
	Survived	Died	Survived	Died
Partial left heart bypass	37	8	65	8
External shunt	13	2		
Hypothermia	0	3	11	4
Homograft	0	1	26	4
Prosthetic graft	54	8	57	6
Direct anastomosis	7	3	14	1

Despite all the "characteristic" clinical and roentgenographic findings, the recognition of aortic injury is often delayed or missed. Commonly, coexisting injuries to other organs[30,32] may either mask the signs of aortic injury or divert the physician's attention away from the diagnosis of rupture of the aorta (Table 3). Paraplegia, frequently due to spinal cord injury; oliguria or anuria, often due to hypovolemia; chest pain, dyspnea, hemothorax, and lung contusion, often due to rib or sternal fractures, can all be caused by aortic rupture. Traumatic rupture of the aorta may also occur without obvious external injury.[11] For these reasons, the possibility of this injury must always be entertained, and careful evaluation of the patient with multiple traumatic injuries should include all body systems, not just those overtly damaged. Attentive and frequent follow-up physical examinations and chest roentgenograms are also very important in the evaluation and treatment of the patient with blunt injuries.

Once the diagnosis of aortic rupture is strongly suspected, confirmatory aortography should be obtained. Percutaneous transaxillary,[35] transbrachial,[14,15,31] or retrograde transfemoral aortography,[6,38] establishes the diagnosis and the site of rupture of the aorta and/or the other great arteries. Extravasation of radiopaque material, with aneurysm formation at the site of rupture of the aorta, and one or two linear intraluminal filling defects, are the typical aortographic findings of acute aortic rupture.[37]

The danger of exsanguination is constantly present in patients who survive the initial injury. For this reason, repair of the rupture should be performed as soon as the diagnosis is confirmed. However, coexisting intra-abdominal injuries, if the patient's condition permits, should be repaired before thoracotomy, since they may interfere with the effectiveness of bypass. The results of the surgical correction of this lethal injury are rewarding (Table 4).

Since the first reported successful early repair of traumatic rupture of the aorta by Passaro and Pace in 1959,[29] many technics have been described. All of them have, as an ultimate goal, the prevention of ischemic spinal cord injury from cross clamping of the aorta during repair of the rupture (Table 5).

For repair of this lesion in the acute stage we have successfully used femoral vein to femoral artery partial cardiopulmonary bypass.[7,8] This technic does not have the problems associated with left atrial cannulation, in that the perfusion lines are away from the main operative field, and partial bypass[8] may be instituted at any time if extensive mediastinal hematoma or sudden hemorrhage should make dissection extremely hazardous without extracorporeal support. An additional advantage is offered in the rare patient who has suddenly developed free aortic rupture at the onset of operation. A second team may initiate partial bypass while thoracotomy and aortic cross clamping are performed.

Temporary local external shunt with tygon tubing primed with 30 ml. of sterile 0.9% saline solution containing 1000 units of heparin[21,23] has been used by us only in chronic aneurysms resulting from rupture of the aorta and in the management of penetrating thoracic aortic wounds.

Guanethidine and reserpine have been used in the management of patients with rupture of the aorta[4] and might be an excellent adjunct in the management of those with posttraumatic acute aortic rupture when other injuries or coincident infection dictate delay of corrective surgery.

Although direct anastomosis of the ruptured aorta has been strongly advocated and successfully accomplished by several authors,[1-3,5,9,22] the vast majority of early and late repairs have been accomplished with the use of prosthetic grafts (Table 5). The retraction of the two ends of the ruptured aorta, the extensive mediastinal hematoma, the occasional friability of the injured aortic wall, and the surrounding reaction usually necessitate the use of a graft to bridge the gap.[23]

Summary

Six patients with rupture of the aorta secondary to blunt trauma have been treated at Emory University Hospitals within the past 4 years. These cases are reviewed along with all previous surgically treated cases of traumatic aortic rupture reported in the English literature. From this review, it appears that the history of severe trauma associated with the triad of pulse amplitude difference between upper and lower extremities, upper extremity hypertension, and widening of the mediastinal shadow has been the most frequently found diagnostic sign of rupture of the aorta. When this diagnosis is strongly suspected, confirmatory aortography should be performed immediately. Repair of these lesions should be accomplished as soon as possible, preferably under partial cardiopulmonary bypass or with temporary shunt bypass of the involved aortic segment.

References

1. Alley, R. D., VanMierop, L. H. S., Li, E. Y., Kausel, H. W. and Stranahan, A.: Traumatic Aortic Aneurysm: Graftless Excision, Anastomosis. Arch. Surg. (Chicago), **83**:300, 1961.
2. Alley, R. D., VanMierop, L. H. S., Li, E. Y., Kausel, H. W. and Stranahan, A: Traumatic Aortic Aneurysm: Excision and Anastomosis Without a Graft. Dis. Chest, **43**:200, 1963.
3. Alley, R. D., VanMierop, L. H. S., Li, E. Y., Kausel, H. W. and Stranahan, A.: Traumatic Aortic Aneurysms. Four Cases of Graftless Excision and Anastomosis. Ann. Thorac. Surg., **2**:514, 1966.
4. Aronstam, E. M., Gomez, A. C., O'Connell, T. J., Jr. and Geiger, J. P.: Recent Surgical and Pharmacologic Experience With Dissecting and Traumatic Aneurysms. J. Thorac. Cardiovasc. Surg., **59**:231, 1970.
5. Beall, A. C., Jr., Arbegast, N. R., Ripepi, A. C., Bricker, D. L. and Diethrich, E. B., Hallman, G. L. Cooley, D. A. and DeBakey, M. E.: Aortic Laceration Due to Rapid Deceleration, Surgical Management. Arch. Surg. (Chicago), **98**:595, 1969.
6. Blazek, J. V.: Acute Traumatic Rupture of the Thoracic Aorta Demonstrated by Retrograde Aortography. Radiology, **85**:253, 1965.
7. Bloodwell, R. D., Hallman, G. L. and Cooley, D. A.: Partial Cardiopulmonary Bypass for Pericardiectomy and Resection of Descending Thoracic Aortic Aneurysms. Ann. Thorac. Surg., **6**:46, 1968.
8. Bricker, D. and Hallman, G. L.: Complete Transection of the Thoracic Aorta: Management of a Case Associated with Massive Total Body Injury. J. Trauma, **10**:420, 1970.
9. Bromley, L. L., Hobbs, J. T. and Robinson, R. E.: Early Repair of Traumatic Rupture of the Thoracic Aorta. Br. Med. J., **2**:17, 1965.
10. Clarke, D. B.: Traumatic Aneurysm of the Innominate Artery at its Origin From the Aortic Arch. Br. J. Surg., **51**:668, 1964.
11. Copeland, G. G.: Traumatic Rupture of the Healthy Aorta Without External Signs of the Cause of Death. JAMA, **63**:1950, 1914.
12. DeMuth, W. E., Jr., Roe, H. and Hobbie, W.: Immediate Repair of Traumatic Rupture of Thoracic Aorta. Arch Surg. (Chicago), **91**:602, 1965.
13. Endress, Z. F.: Traumatic Mediastinal Hematoma. Report of Two Cases. Amer. J. Roentgenol., **70**:576, 1953.
14. Flaherty, T. T., Wegner, G. P., Crummy, A. B., Francyk, W. P. and Hipona, F. A.: Nonpenetrating Injuries to the Thoracic Aorta. Radiology, **92**:541, 1969.
15. Freed, T. A., Neal, M. P., Jr. and Vinik, M.: Roentgenographic Findings in Extracardiac Injury Secondary to Blunt Chest Automobile Trauma. Amer. J. Roentgenol., **104**:424, 1968.
16. Freed, T. A. and Bosher, L. H., Jr.: Arteriographic Demonstration of Laceration of Great Vessels Secondary to Blunt Trauma. Radiology, **90**:88, 1968.
17. Gerbode, F., Baimbridge, M., Osborn, J. J., Hood, M. and French, S.: Traumatic Thoracic Aneurysms: Treatment by Resection and Grafting with the Use of an Extracorporeal Bypass. Surgery, **42**:975, 1957.
18. Goyette, E. M., Blake, H. A., Forsee, J. H. and Swan, H.: Traumatic Aortic Aneurysms. Circulation, **10**:824, 1954.
19. Greendyke, R. M.: Traumatic Rupture of Aorta. Special Reference to Automobile Accidents. JAMA, **195**:527, 1966.
20. Jensen, O. M.: Traumatisk Aorta Ruptur. En Analyse of 68 Fatale Tilfaelde. Nord. Med., **71**:337, 1964.
21. Kahn, D. R., Vathayanon, S. and Sloan, H.: Resection of Descending Thoracic Aneurysms Without Left Heart Bypass. Arch. Surg. (Chicago), **97**:336, 1968.
22. Keen, G., Bradbrook, R. A. and McGinn, F.: Traumatic Rupture of the Thoracic Aorta. Thorax, **24**:25, 1969.
23. Kirsh, M. M., Kahn, D. R., Crane, J. D., Anastasia, L. F., Lui, A. H., Moores, W. Y., Vathayanon, S., Bookstein, J. J. and Sloan, H.: Repair of Acute Traumatic Rupture of the Aorta Without Extracorporeal Circulation. Ann. Thorac. Surg., **10**:227, 1970.
24. Kirsh, M. M., Crane, J. D., Kahn, D. R., Gago, O., Moores, W. Y., Redman, H., Bookstein, J. J. and Sloan, H.: Roent-

genographic evaluation of Traumatic Rupture of the Aorta. Surg. Gynecol. Obstet., **131**:900, 1970.

25. Laforet, E. G.: Traumatic hemomediastinum. J. Thorac. Cardiovasc. Surg., **29**:597, 1955.
26. Malm, J. R. and Deterling, R. A., Jr.: Traumatic Aneurysm of the Aorta Simulating Coarctation. A Case Report. J. Thorac. Cardiovasc. Surg., **40**:271, 1960.
27. McClenathan, J. E. and Brettschneider, L.: Traumatic Thoracic Aortic Aneurysms. J. Thorac. Cardiovasc. Surg., **50**:74, 1965.
28. Parmley, L. F., Mattingly, T. W., Manion, W. C. and Jahnke, E. J.: Nonpenetrating Traumatic Injury of the Aorta. Circulation, **17**:1086, 1968.
29. Passaro, E., Jr. and Pace, W. G.: Traumatic Rupture of the Aorta. Surgery, **46**:787, 1959.
30. Roberts, J. C. and Lord, P. W.: Ruptured Thoracic Aorta. Anesthesia and Post-operative Management in Two Cases. Anaesthesia, **22**:415, 1967.
31. Sanborn, J. C., Heitzman, E. R. and Markarian, B.: Traumatic Rupture of the Thoracic Aorta. Roentgen-pathological Correlations. Radiology, **95**:293, 1970.
32. Schonholtz, G. J. and Jahnke, E. J.: Occult Injury of the Thoracic Aorta Associated with Orthopedic Trauma. J. Bone Joint Surg. **46A**:1421, 1964.
33. Stoney, R. J., Roe, B. G. and Redington, J. V.: Rupture of Thoracic Aorta Due to Closed-chest Trauma. Arch. Surg. (Chicago), **89**:840, 1964.
34. Strassman, G.: Traumatic Rupture of the Aorta. Amer. Heart J., **33**:508, 1947.
35. Symbas, P. N., Pourhamidi, A. and Levin, J. M.: Traumatic Rupture of the Aortic Arch Between Left Common Carotid and Left Subclavian Arteries and Avulsion of the Left Subclavian Artery. Ann. Surg., **170**:152, 1969.
36. Symbas, P. N.: Traumatic Injuries of the Heart and Great Vessels, Springfield, Charles C Thomas, 1972, pp. 151–153.
37. Symbas, P. N.: *op cit.*, 1972, 159.
38. Wagner, J. C. and Miller, J. D. R.: Value of Angiography in Acute Conditions Affecting the Thoracic Aorta. Can. Med. Assoc. J., **103**:57, 1970.
39. Wyman, A. C.: Roentgenologic Diagnosis of Traumatic Aneurysm of the Thoracic Aorta. Arch. Surg. (Chicago), **66**:656, 1953.

Omental, Mesenteric, and Retroperitoneal Cysts:

A Clinical Study of 33 New Cases

ALLAN R. WALKER, M.D., THOMAS C. PUTNAM, M.D.

From the Department of Surgery, University of Rochester School of Medicine and Dentistry, Rochester, New York

CYSTIC LESIONS of the omentum, mesentery, and retroperitoneum are uncommon lesions which are seldom diagnosed prior to operation. Several authors[4,14] have indicated that these lesions may be grouped in the same category since they are similar, both embryologically and pathologically.

Barr and Yamashita[1] stated that "preoperative diagnosis is infrequently made because they are not usually considered in the differential diagnosis". We have undertaken to review our experience with these lesions emphasizing clinical features rather than pathologic features. By placing emphasis on the clinical aspects of these lesions, we feel that a preoperative diagnosis or at least a high index of suspicion may be possible more frequently than has been previously reported. This study is based on a review of charts from the University of Rochester's Strong Memorial Hospital and four local affiliated teaching hospitals during the period from 1955 to 1970. We have excluded lesions which may be classified as intestinal duplications.

Results

Thirty-three new cases of omental, mesenteric, and retroperitoneal cysts are reported. The diagnosis was proven at operation in all cases.

There were six males and 27 females, with an age range of 1 day to 76 years. Analysis by age (Table 1) revealed a relatively even distribution throughout all decades. In addition to the six cases in the first decade, there were two other instances in the pediatric age group (15 years) making a total of eight cases (24%) in children.

Of the 33 cases, there were 13 omental cysts, 18 mesenteric cysts and two retroperitoneal cysts. Since case records were not available for three women with mesenteric cysts, the remaining discussion will concern only the 30 patients for whom records were available. The clinical presentation of these 30 cases is shown graphically in Figure 1.

The lesions were incidental findings at operation in 12 of the 30 patients. Of these, eight were omental, three were mesenteric, and one was retroperitoneal. In the other 18 instances (Table 2), operation was performed for symptoms or signs directly attributable to the lesion. In five of the 18 patients, surgical treatment was performed on an emergency basis, due to the presence of acute intra-abdominal conditions. In the remaining 13 patients, operation was elective.

The five emergent cases included two adults with apparent acute appendicitis, one of whom (Case 12) had a mesocolic cyst with recent hemorrhage and inflammation and one (Case 8) who had an omental cyst which had undergone torsion. There were two infants with large omental cysts that had ruptured with hemorrhage, showing a clinical picture of abdominal distention and intra-abdominal bleeding. One was a neonate (Case 1) and the other was aged 23 months (Case 4). The fifth emergent instance (Case 6) occurred in a 6-year-old girl who showed a clinical picture of small bowel obstruction secondary to a large mesenteric cyst.

Of the 13 patients operated upon electively, ten had mesenteric cysts. Eleven of the 13 had palpable abdominal masses, and two were children with large cysts causing generalized abdominal distention. In six cases, a mobile, non-tender abdominal mass was found on routine examination and no symptoms were present. Histories of pain varying in duration from 4 days to 5 years were elicited from the other seven patients. The pain was intermittent in three patients and steady in

---

Submitted for publication June 19, 1972.

Request reprints: Allan R. Walker, M.D., c/o Department of Surgery, Highland Hospital, Rochester, New York 14620.

TABLE 1. *Distribution of Cases by Age and Location*

Decade	Omental	Mesenteric	Retroperitoneal	Total
0–10	4	2		6
11–20	0	2		2
21–30	2	2		4
31–40	2	3		5
41–50	2	2	1	5
51–60	0	4	1	5
61–70	2	2		4
71–80	1	1		2
				33

four. The pain was accompanied by nausea and vomiting in three patients.

X-ray examinations of various types were carried out in 15 of the 18 patients in whom the cyst was considered to be the primary source of symptoms and/or signs. Plain films of the abdomen were reported in 11 patients and showed positive findings in ten. Nine patients had evidence of a soft tissue mass and one demonstrated a pattern typical of small bowel obstruction. Displacement of bowel by the mass was noted on the plain films in three and calcifications of the mass was seen in five patients. An upper gastrointestinal series was done in seven patients, and seven patients had barium enema X-rays performed. Two of these patients underwent both studies. These studies demonstrated extrinsic compression or displacement of some portion of the gastrointestinal tract in five of the seven patients in each group. Intravenous pyelography was done in six patients. This study was normal in four patients, one had a displaced ureter and another patient had a unilateral hydro-ureter and hydro-nephrosis.

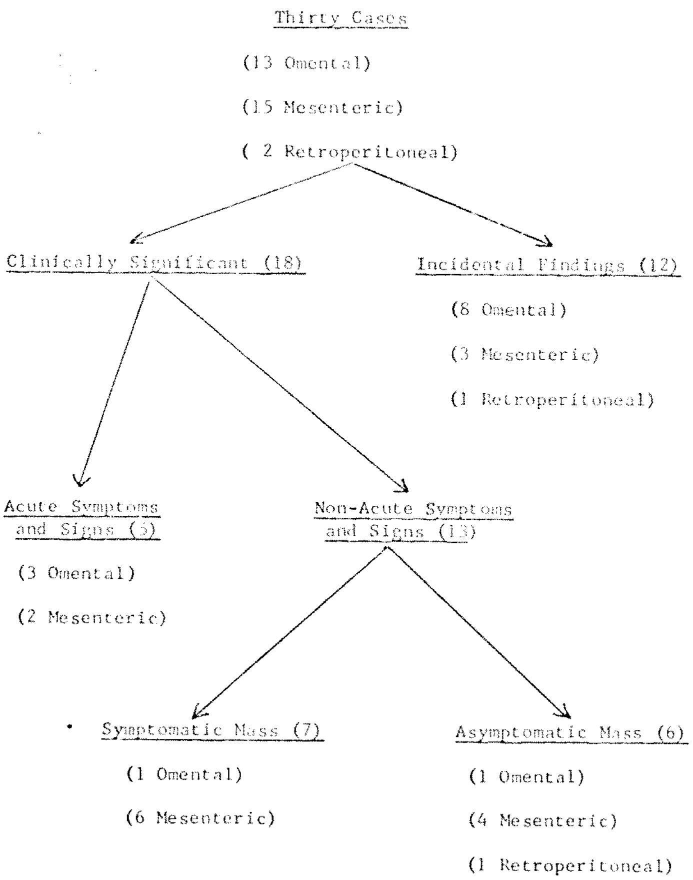


FIG. 1. Summary of clinical presentation of 30 cases.

The pathologic features of these cysts showed a marked variability. There were 23 unilocular cysts, including 12 of the 13 omental cysts, and only seven multilocular. Lining cells were present in 16 patients, absent in ten and not reported in four. The lining cells, when present, varied from flattened, to cuboidal, to columnar epithelium.

There were seven cysts with evidence of bleeding. Three of these were acute with bright red blood, while in the remaining four patients, the bleeding was old and manifested by brown fluid in the cyst.

The size range varied from 1.0 cm. to large cysts filling the entire abdominal cavity. In general, the smallest cysts were omental with eight of the 13 being 4.0 cm. or less in greatest diameter. In contrast to this, the smallest of the mesenteric cysts was 3.0 cm. in diameter and 11 of the 15 were between 6 and 15 cm. in greatest diameter.

In two patients the lesions recurred. In one (Case 3), a recurrent cyst developed in the omental remnant 9 months after excision of a huge omental cyst. In the second (Case 15), a patient developed multiple recurrent mesenteric cysts ten years after excision of a retroperitoneal cyst.

Discussion

History and Incidence

The first report of a mesenteric cyst is commonly ascribed to a Florentine anatomist, Beneviene, who related the finding of a cyst of the small bowel mesentery during an autopsy in 1507. The first surgical excision was reported in 1880 by Tillaux, and since that time numerous case reports have been presented. Loeb[15] reviewed the literature on mesenteric cysts in 1941 and estimated that 550–600 cases had been reported, and it is likely that there are now at least 700–750 cases in the literature.

Omental cysts were not described until the report of Gairdner in 1852, and are less common than the mesenteric variety. In 1964, Oliver[17] estimated the total number of cases of omental cysts to be 150 and he reported an additional 13 cases.

Mesenteric cysts have been estimated to be three to ten times more common than omental cysts,[2] although on the basis of the numbers of reported cases, the ratio may be set at 4.5 to one.

The rate of incidence of both cyst types has been

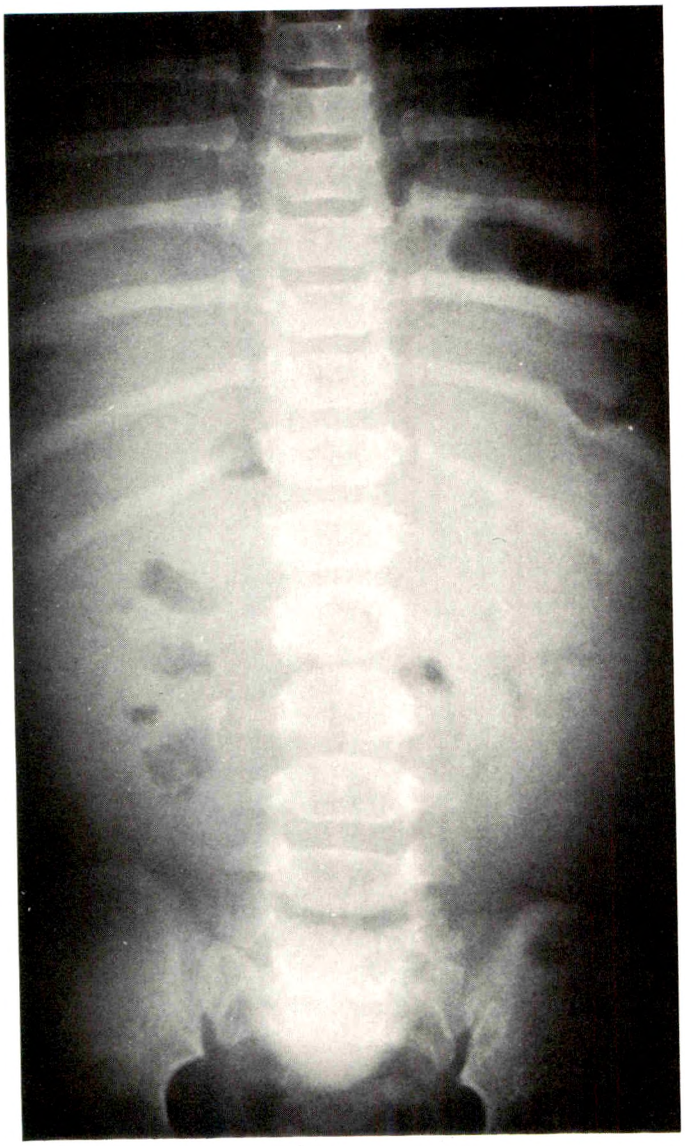


FIG. 2A. Plain A-P film of an 11-month-old girl (Case 3) with fluid abdominal distention. Film revealed diffuse haziness suggestive of ascites.

variously reported from one case per 27,000 hospital admissions[12] to one per 100,000 admissions.[18] In this series the rate was one case per 35,400 admissions.

These lesions are generally reported to be more common in females and this fact was supported by this series which showed that 82% occurred in females.

Pathology

Pathologically, these lesions are generally single, although multiple occurrences have been reported. They may be unilocular or multilocular and contain fluid which may range from a clear, straw-colored liquid to a thick cheesy-white material which is thought to be inspissated lymph fluid. They may exhibit evidence of bleeding into the cyst cavity, either recent or old. Calcification may occur but is generally reported to be a rare event. There is no apparent correlation between calcification and previous bleeding. Only one of the five cysts in this series with calcification showed any evidence of recent or old bleeding.

Lining cells may or may not be present and may range from flattened endothelial cells to low cuboidal or high columnar epithelial cells.

Malignant change has been reported, but is uncommon. Hardin and Hardy[12] indicate that the malignancies are usually low grade sarcomas and carry a good prognosis if properly excised.

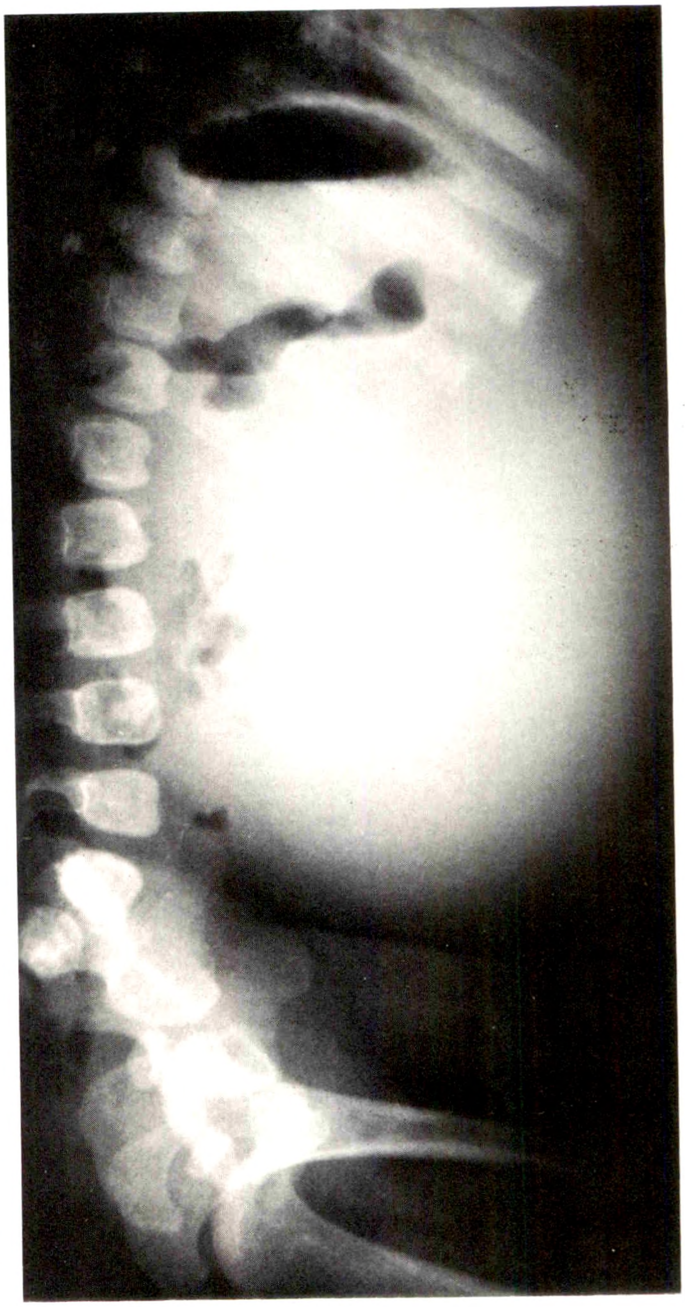


FIG. 2B. Lateral view of same patient demonstrating posterior displacement of intestinal gas, a finding indicative of intra-abdominal cyst.

TABLE 2. *Summary of Findings of 18 Patients with Clinically Significant Lesions*

Case	Age & Sex	Symptoms and Signs	X-ray	Pathology	Location and Size	Remarks
1	1 day F	Abdominal distention, pallor, lethargy, bloody fluid on paracentesis.	None.	Unilocular cyst—ruptured with hemorrhage.	Omentum—large cyst filling abdominal cavity.	
2	14 wk. F	Mobile right flank mass on routine physical examination.	*Plain film*—5 cm. calcific density in right lower quadrant. *Upper GI series*—small bowel displaced to left.	Unilocular cyst no lining cells old bleeding.	Omentum—4 × 6 cm.	
3	11 mo. F	Abdominal distention–Recurrent abdominal pain and vomiting for 3 months.	*Plain film*—Diffuse abdominal haziness. *Lateral view of abdomen*—Bowel gas displaced posteriorly *Upper GI series*—Displacement of small bowel to left.	Multilocular cyst columnar epithelial lining.	Huge omental cyst filling abdominal cavity.	Patient returned 9 months later with recurrent cyst of omental remnant.
4	23 mo. M	Lethargy and pallor of sudden onset. Abdominal distention.	*Plain film*—Upward displacement of bowel. *Barium enema*—Displacement and extrinsic compression of cecum and sigmoid colon	Unilocular cyst with mesothelial lining ruptured with hemorrhage.	Omentum—Huge cyst filling abdominal cavity.	
5	5 yrs. M	Abdominal distention for 2 to 3 weeks. Right upper quadrant pain for 4 days.	*Plain film*—Upward displacement of transverse colon by mass with calcified rim. *Barium enema*—Extrinsic compression. *IVP*—Right hydronephrosis and hydroureter.	Multiloculated cyst. No lining cells.	Jejunal mesentery 25 cm.	
6	6 yr. F	Abdominal and pain vomiting for 3 days. Abdominal distention.	*Plain film*—Gas pattern characteristic of small bowel obstruction.	Unilocular cyst. No. lining cells.	Jejunal mesentery 10 cm.	
7	13 yr. F	Intermittent abdominal pain and vomiting for 2 years. Abdominal mass.	*Upper GI series* and *Barium enema*—Extrinsic compression of bowel by central mass.	Unilocular cyst with "chocolate" fluid. No lining cells.	Transverse Mesocolon 15 cm.	

Etiology and Classification

As early as 1916, it was suggested by Hadley[10] that "it seems more than probable that the group of abdominal tumors classified as chylous cysts do not all have the same origin . . ."

The etiology of these lesions has been subject to much discussion in the literature over the years, with the principal debate centering around the question of of whether or not these lesions are congenital. Some writers have claimed that all of these cysts are congenital with some not being found until adulthood. Others cite the relatively low incidence in childhood, such as the 25% reported by Burnett, *et al.*,[5] as evidence that they are not congenital. It is now recognized that there is no single etiologic mechanism involved in the development of all these cysts. The literature contains several examples of cysts which are definitely congenital, but there are also a large number of definitely acquired cysts which have been reported.

In 1950, Beahrs *et al.*,[3] proposed the following etiologic classification for these lesions:

A. *Embryonic and Developmental Cysts*
   including enteric, urogenital and dermoid cysts, as well as cysts arising from embryonic defects in lymph tissue.
B. *Traumatic or Acquired Cysts*
   No lining cells are seen.
C. *Neoplastic Cysts*
   Benign and malignant including lymphangiomata.
D. *Infective and Degenerative Cysts*
   of mycotic, parasitic or tuberculous origin.

We believe this to be a complete and logical classifi-

TABLE 2. (*Continued*)

Case	Age & Sex	Symptoms and Signs	X-ray	Pathology	Location and Size	Remarks
8	24 yr. F	Right lower quadrant pain for several hours. Right lower quadrant tenderness and spasm.	None.	Unilocular cyst with torsion.	Omentum 7 × 5 × 4 cm.	
9	28 yr. F	Abdominal pain, nausea and vomiting for 2 weeks. Mobile mass in left mid-abdomen.	*Barium enema*—Negative. *IVP*—Displaced left ureter.	Multiloculated cyst. No lining cells. Brownish fluid.	Jejunal mesentery 15 cm.	
10	34 yr.	Lower abdominal pains for 5 years. Left flank ache for 1 month mobile left upper quadrant cystic mass.	*Plain film*—Left upper quadrant mass with calcified rim.	Unilocular cyst. No lining cells.	Proximal jejunal mesentery—6 cm.	
11	50 yr. M	Asymptomatic left lower quadrant mass on routine examination.	*Plain film*—Calcified left lower quadrant mass.	Unilocular—No lining cells.	Mid-jejunal mesentery 6 × 4 cm.	
12	52 yr. M	Right lower quadrant pain for several hours. Right lower quadrant guarding and tenderness.	None.	Unilocular cyst. No lining; recent hemorrhage and inflammation.	Transverse Mesocolon 4 × 7 cm.	
13	55 yr. M	Large mid-abdominal, mobile mass for 4 years.	*Plain film*—Soft tissue mass. No bowel displacement.	Unilocular cyst. No lining cells.	Small bowel mesentery 25 cm.	
14	58 yr. F	Right lower quadrant mass on routine physical examination.	*Barium enema*—Extrinsic pressure on cecum by calcified mass.	Multiloculated cyst. Flattened epithelial lining.	Retroperitoneal cyst medial to cecum 10 × 12 × 5 cm.	
15	60 yr. F	Left abdominal mass—asymptomatic.	*Plain film*—Soft tissue density in abdomen.	Multiloculated cysts. Cuboidal and columnar epithelium.	Multiple mesenteric cysts filling abdominal cavity.	Previous excision of retroperitoneal cyst.
16	60 yr. F	Left abdominal mass on routine physical examination.	*Plain film*—Abdominal mass. *Upper GI series*—Displacement of jejunum.	Unilocular cyst. No lining cells.	Jejunal mesentery 10 × 12 cm.	
17	62 yr. F	Abdominal pain for 6 months. Tender upper abdominal mass.	*Barium enema*—Extrinsic compression of transverse mesocolon.	Unilocular cysts. No lining cells.	Transverse mesocolon 7 cm.	Previous vagotomy and pyloroplasty—no cyst at that time.
18	66 yr.	Pain in right side of back for 1 month. Soft, mobile, epigastric mass.	*Upper GI series*—Compression of lesser curvature.	Unilocular cyst. No lining cells.	Gastro-hepatic mesentery 14 cm.	

cation which is consistent with currently available factual information. As suggested by Beahrs,[3] this classification also serves to clarify much of the confusion resulting from the use of such terms as "chylous" or "lymphatic" cysts.

Diagnosis

The diagnostic features of clinically significant omental and mesenteric cysts appear to be a function of size, location, and presence or absence of complicating factors such as hemorrhage, torsion, infection, rupture, or pressure on adjacent structures.

It is obvious that a very small cyst may be asymptomatic and nonpalpable and therefore discovered only as an incidental finding at operation. In this series, there were 12 (40%) such cases. It is of interest that the majority of these (8/12) were omental in location; however, the size of the lesion rather than the location, appears to be a more important factor. Of the 12 cysts found incidentally only three were larger than 4 cm. and the smallest of the clinically significant cysts was 6 cm. in diameter.

The symptoms and signs caused by omental and mesenteric cysts are variable, and none may be considered pathognomonic. Patients with clinically important (*i.e.*, non-incidental) cysts may be classified into two basic groups, acute and non-acute.

The acute group includes those patients with acute symptoms which require operation on an emergency basis.

In 1964, Oliver[17] reviewed the subject of acute abdominal crisis caused by omental cysts. In addition to the three cases in his series, he was able to find only

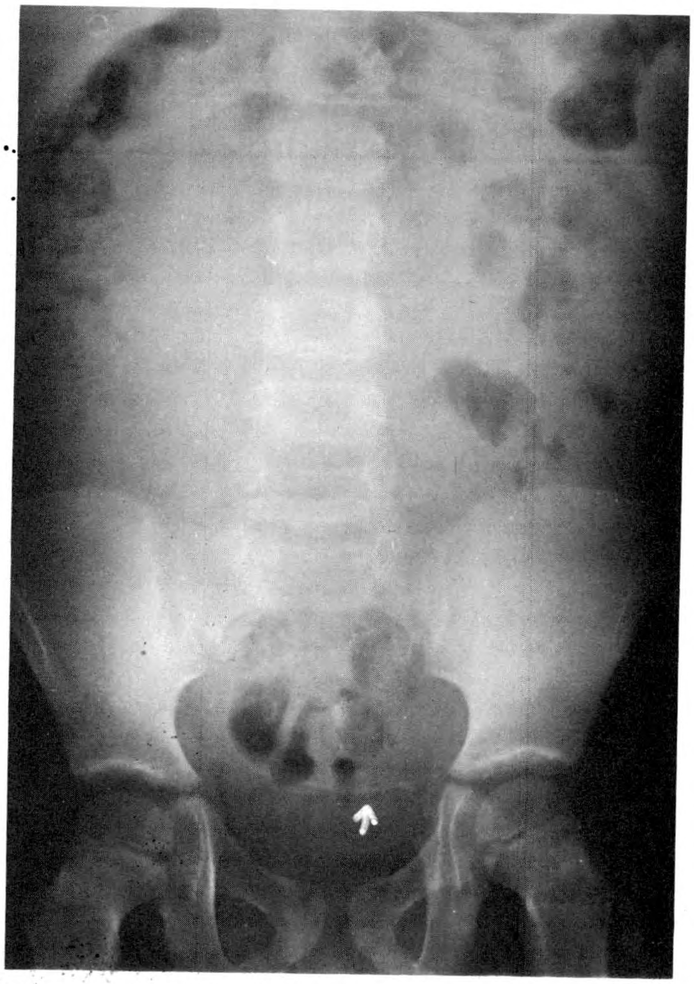


FIG. 3A. Plain A-P film of a 5-year-old boy (Case 5) showing mass defect with calcified inferior rim.

15 other reports in the literature for a total of 18 cases. This is approximately 10 per cent of all the omental cysts reported. In 93 per cent of these cases, the preoperative diagnosis was acute appendicitis; however, it was stressed that the clinical picture was non-specific. The tenderness was usually diffuse and masses were not usually palpable. It is of interest to note that the clinical picture of an acute surgical abdomen caused by omental cysts is a disease of children almost exclusively. Of the 18 cases summarized by Oliver, the oldest was 24 years and only three patients were over ten years of age. In our series, there were three such patients with ages one day, 23 months, and 24 years. As reported by Oliver, the most common complication is torsion (8/18) with infection (6/18) being next most common.

Mesenteric cysts are probably an even rarer cause of the acute abdomen than omental cysts. Two such cases are seen in this series, one of small bowel obstruction and the other a case of hemorrhage and inflammation. Both of these complications have been reported previously by other authors.[6,7,11]

In both omental and mesenteric cysts which present as acute surgical emergencies, the mass may not be palpable because of abdominal rigidity. Nausea, vomiting and anorexia are commonly seen, as are coincidental leukocytosis and fever. Because of similarity to many more common conditions, preoperative diagnosis is rare in the cases with acute symptoms.

The non-acute group includes those patients with asymptomatic abdominal masses and those with chronic abdominal symptoms with or without a mass. These masses are usually described as being smooth, round, non-tender, and mobile. Mesenteric cysts are often said to be more mobile in a transverse plane than in a cephalo-caudad plane, while omental cysts are very mobile in all directions. Lesions which seem cystic and tethered to the pelvis are most likely to originate from the uterus, ovaries and urinary bladder.

Some authors[1,9] feel that these lesions most commonly occur as slowly enlarging painless lesions, while other investigators[5] have found pain to be a more predominant component of the clinical picture. In this series, pain was observed in 7/12 (60%) of the non-acute cases. Six of these were mesenteric in location.

The character of the pain will, of course, depend on the mechanism of its production. Steady pain may be a result of stretching the overlying peritoneum or of traction on the root of the mesentery. Intermittent crampy pain is usually thought to be a result of partial

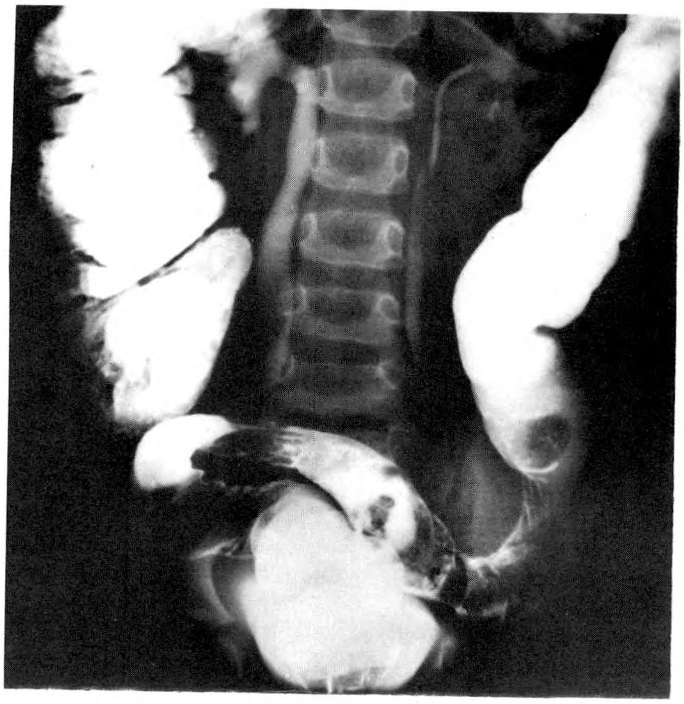


FIG. 3B. Combined barium enema X-ray and intravenous pyelogram of same patient demonstrating right hydronephrosis and hydroureter and extrinsic compression of colon.

obstruction of the gastrointestinal tract by extrinsic pressure. Generally speaking, the pain is of low-grade intensity and not related to meals. Nausea and vomiting may occur, but are generally thought to be less common.

Radiographic studies may be of utmost importance in the preoperative diagnostic work-up. Berger and Rothenberg[4] stated that "the correct diagnosis would have been made more often in our series of cases had the surgeons resorted more frequently to X-ray investigations". The demonstration of these cystic lesions is dependent upon their size, density, affect on adjacent organs, and calcification of the wall of the cyst when present.

A plain film of the abdomen is seldom of great assistance in confirming the diagnosis, although evidence of a soft-tissue mass is common and displacement of the bowel may be present. Ladd and Gross[13] have pointed out the value of a plain lateral view of the abdomen which may reveal that the mass in question lies anterior to the intestines, a finding which suggests the possibility of an omental cyst (Figs. 2A and 2B). These findings made possible a correct preoperative diagnosis of omental cyst in Case 3. Calcification of the cyst wall and/or contents may also be noted on plain films (Fig. 3A) but is generally reported to be a rare finding.[19] In this series, there were five cases that showed calcification.

The demonstration of displacement of the bowel by an extrinsic mass may be more consistently obtained by contrast studies, *e.g.* upper gastrointestinal series and barium enema X-ray. Bowel displacement was seen in over 70 per cent of the patients in whom these contrast studies were done in this series (Fig. 3B). Even if negative, these studies are helpful in that they rule out primary disease of the intestinal tract.

Similarly, intravenous pyelography, which should be performed in all cases of abdominal mass, rules out renal lesions. Obstruction or displacement of ureters or compression of urinary bladder (Fig. 3B) may be demonstrated. Selective superior mesenteric angiography has been carried out in one case of a large mesenteric cyst[16] but this was a normal study and not thought to be of any diagnostic value.

Summary

A series of 33 patients with omental, mesenteric, and retroperitoneal cysts is presented with an emphasis on the clinical features.

There were six males and 27 females, ranging in age from 1 day to 76 years. Clinical data are presented for 30 of the patients. Twelve had cysts discovered as incidental findings at operation. Five patients with symptoms and signs of an acute abdomen required emergency operation, and preoperative diagnosis would have been difficult. Thirteen patients with chronic symptoms and signs, operated upon electively, had preoperative findings suggestive of cyst. There are no pathognomonic clinical characteristics which permit an accurate preoperative diagnosis in these lesions; however, we feel that retroperitoneal cysts (including mesenteric and omental) should be suspected in any patient with a mobile abdominal mass, with or without chronic pain, and in whom plain and contrast radiographic studies of the abdomen demonstrate the mass to be extrinsic to the alimentary and urinary tracts.

References

1. Barr, W. B. and Yamashita, T.: Mesenteric Cysts. Am. J. Gastroenterol., 41:53, 1964.
2. Beahrs, O. M. and Dockerty, M. D.: Primary Omental Cysts of Clinical Importance. Surg. Clin. N. Am., **302**:1073, 1950.
3. Beahrs, O. M., Judd, E. S. and Dockerty, M. B.: Chylous Cyst of the Abdomen. Surg. Clin. N. Am., **302**:1081, 1950.
4. Berger, L. and Rothenberg, R. E.: Cysts of the Omentum, Mesentery, and Retroperitoneum. Surgery, **5**:522, 1939.
5. Burnett, W. E., Rosemond, G. P. and Bucher, R. M.: Mesenteric Cysts. Arch Surg., **60**:699, 1950.
6. Fahmy, A., Smith, R., Garner, M. T.: Frazier, H. M. and Walker, M., Mesenteric Cyst Presenting as an Acute Surgical abdomen. Am. Surg., **32**:654, 1966.
7. Fish, J. C., Fair, W. R. and Canby, J. P.: Intestinal Obstruction in the Newborn—An Unusual Case Due to Mesenteric Cyst. Arch. Surg., **90**:307, 1965.
8. Gordon, R. B., Capetillo, A. and Principato, D. J.: Angiographic Demonstration of Lymphatic Cyst of the Mesentery. Am. J. Roentgenol., **1042**:870, 1968.
9. Greene, R. E.: Abdominal Mass in Infancy. JAMA, **293**:1095, 1967.
10. Hadley, M. N.: The Origin of Retroperitoneal Cystic Tumors. Surg. Gynecol Obstet., **22**:174, 1916.
11. Hardin, W. J., Elliot, R. L., Wesson, R. L. and Lowicki, E. M.: Hemorrhagic Mesenteric Cyst Simulating an Acute Abdomen. Am. Surg., **33**:733, 1967.
12. Hardin, W. J. and Hardy, J. D.: Mesenteric Cysts. Am. J. Surg., **119**:640, 1970.
13. Ladd, W. E. and Gross, R. E.: Abdominal Surgery of Infancy and Childhood. W. B. Saunders, Philadelphia, 1947, p. 233.
14. Lahey, F. H. and Eckerson, E. B.: Retroperitoneal Cysts. Ann. Surg., **100**:231, 1934.
15. Loeb, M. J.: Mesenteric Cysts. N.Y. State J. Med., **412**:1564, 1941.
16. Oh, C., Danese, C. A. and Dreiling, D. A.: Chylous Cysts of Mesentery. Arch. Surg., **94**:790, 1967.
17. Oliver, G. A.: The Omental Cyst: A Rare Cause of the Acute Abdominal Crisis. Surgery, **56**:588, 1964.
18. Sprague, N. F.: Mesenteric Cysts. Am. Surg., **26**:42, 1960.
19. Vaughn, A. M., Lees, W. M. and Henry, J. W.: Mesenteric Cysts. Surgery, **23**:306, 1948.

Delayed Cutaneous Hypersensitivity Reactions to Extracts of Malignant and Normal Human Breast Cells

CRANDALL ALFORD,* ARIEL C. HOLLINSHEAD,† RONALD B. HERBERMAN**

From the Department of Surgery, George Washington University Medical Center, Washington, D.C.

MOST ANIMAL TUMORS studied possess antigens that are present in malignant cells but absent in normal cells.[18] These tumor specific antigens may elicit a humoral and/or cellular immune response in the animal. Certain human malignancies also have tumor associated antigens which can produce an immune reaction.[10]

The natural history of human mammary cancer suggests that host responses are significant.[1] Morphological changes in the primary tumor and draining lymph nodes are used as evidence for immune reactions to mammary cancer.[3,4] Previous reports indicate antigenic changes in human mammary cancer[8] and antibodies to tumor associated antigens have been found in the sera of patients with this disease.[5,20] In addition, virus-like particles resembling murine RNA oncogenic viruses have been seen in specimens of human milk and in tumors of patients with mammary cancer.[16] These ultra-structural and other immunological findings indicate certain similarities in neoplasia of the breast in women and mice.[17]

In the present study, delayed hypersensitivity skin tests were performed in an attempt to detect cellular immune reactions in patients with mammary cancer.

Materials and Methods

Patient Selection

All patients studied had a complete examination including appropriate laboratory determinations. The patients were staged according to the following criteria: in stage I patients, the tumor was confined to the primary site; stage II patients had regional node involvement. All stage I and II patients had operable lesions. Stage III patients had systemic metastases. Of the 21 patients with cancer of the breast 18 were stage I and II and had undergone definitive surgical treatment 7 to 30 days prior to skin testing. The remaining three had disseminated mammary cancer (Stage III) and two were receiving hormone therapy. Four patients with benign mammary disease were studied: three were operated on for fibrocystic disease and one had a reduction mammoplasty. Of the patients with cancer not originating in the breast, two were stage I or II and three were stage III.

Tissue Preparation

Sterile technics were used throughout. Tumor and normal breast were finely debrided so that grossly viable tissue was used. Normal breast tissue and pectoralis muscle were removed as far distant from the primary tumor site as possible. Tissues were minced with scissors and pressed through a #60 stainless steel mesh sieve to obtain a single cell suspension. The cells were then counted in a hemocytometer; 10^7 to 10^9 cells were used. A smaller number of cells was not satisfactory, unless pooled with another similar tissue, because of the low protein yield. Cell membrane extracts of the tissues were then prepared using the method of Davies[6] and Mann *et al.*[15] Solubilization of the membrane preparations with low frequency sonication and fractionation by Sephadex gel filtration have been described.[12] Sephadex pools were concentrated using

---

Submitted for publication April 17, 1972.

* Department of Surgery, George Washington University Medical Center, Washington, D.C.

† Laboratory for Virus and Cancer Research, George Washington University Medical Center.

** Cellular & Tumor Immunology Section, Laboratory of Cell Biology, National Cancer Institute, Bethesda, Maryland.

Diaflo ultrafiltration. Protein determinations were made by the method of Lowry.[14]

Skin Tests

To assess the ability of the patients to manifest delayed hypersensitivity reactions, mumps antigen (Eli Lilly & Co, Indianapolis, Ind.) and Varidase (Streptokinase-Streptodornase 50 μ, Lederle Lab., Pearl River, N.Y.) were injected intradermally prior to skin testing with tissue extracts. Only patients with a positive skin test to either antigen were included. Tests performed in the immediate postoperative period were often negative but reverted to positive after 1 week. Forty-eight hours after the first skin test, 0.1 ml. of membrane and soluble fractions of the membranes were injected intradermally. All tests were performed on the skin of the upper back and were read at 15 minutes, 24 and 48 hours. Induration of 5 mm. or more at 48 hours was considered positive. Biopsies of positive reactions showed histological features consistent with a delayed hypersensitivity reaction. As controls, patients were also tested with buffer solutions from Sephadex columns. The protein range for the membranes extracts was 80-200 μg./0.1 ml. with an average of 100 μg./0.1 ml. The soluble fractions had a range of 5-100 μg./0.1 ml. with an average of 40 μg./0.1 ml.

Membranes

Mammary Cancer Patients. Three of nine patients with cancer of the breast tested with autologous tumor membranes were positive. Four patients were also tested with autologous membranes prepared from grossly normal breast tissue from the same mastectomy specimen. These tests were all negative (Table 1). Three of four mammary cancer patients had delayed hypersensitivity skin reactions to allogeneic mammary cancer membranes but had no reaction to allogeneic normal breast membranes derived from the same breast. One of five patients had a positive skin test to allogeneic normal breast membranes from a patient with fibrocystic disease and one of eight patients was positive to autologous pectoralis muscle membranes from a mastectomy specimen.

Control Patients. Five patients with solid tumors other than mammary cancer were tested (three head and neck, one melanoma and a colon cancer). Four were skin tested with mammary cancer membranes, three with normal breast membranes from the same mastectomy specimen and two with normal breast membranes from fibrocystic disease patients. There were no positive responses in any of these patients (Table 1).

Three patients with fibrocystic disease and two patients with other benign conditions did not respond to the membranes of normal breast tissue from patients with fibrocystic disease (Table 1).

Therefore, six of 13 patients with mammary cancer were positive to their own or allogeneic cancer membranes and none of eight patients were positive to either autologous or allogeneic normal breast membranes from the same mastectomy specimen. No patients with other types of cancer gave a positive skin test to any of these breast membrane preparations.

It is of interest that the three stage III patients with mammary cancer were positive to the mammary cancer membranes while only three of 10 patients with stage I and II were reactive. These patients with stage III disease had an unusual tumor-host relationship in that they had a tumor-free interval of over 5 years from definitive therapy to evidence of recurrent disease. Two patients were skin-tested shortly after additive hormonal therapy was started and had partial objective tumor regression that lasted 7 to 18 months before relapsing. The third patient was tested 2 months after therapeutic oophorectomy when no clinical disease was apparent and is still in remission 16 months later with

TABLE 1. *Delayed Hypersensitivity Skin Reactions to Breast Tissue Membrane Extracts*
(Number of positive tests over the number of patients tested)

Type of Patient	Ca Breast	N-Ca Breast**	N-N Breast*	Muscle-Mastectomy Specimen
Cancer				
Breast				
autologous	3/9	0/4	------+	1/8
allogeneic	3/4	0/4	1/5	ND***
Other Cancer	0/4	0/3	0/2	ND

Benign Disease				
Breast	------	------	/03	------
Other	------	------	0/2	

* Normal breast tissue from patients with benign breast disease
** Normal breast tissue from mastectomy specimen
*** ND = Not done
-----+ Not applicable or would involve tests with tissues from patients with malignant diseases in benign conditions.

P, 24,764.

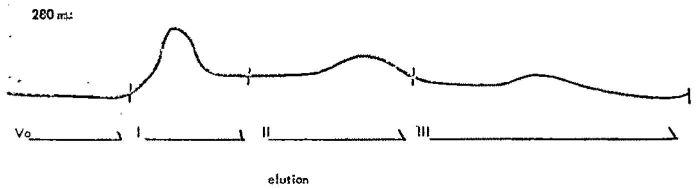


FIG. 1. Separation of mammary cancer cell membrane sonicate on Sephadex G-200 (reactive fraction II is between 35,000 mw and 120,000 mw with a protein peak which ranged between 42,000 to 56,000 for nine different separations). Fraction II contains about half of the total soluble protein and has fewer aromatic amino acids than fractions I and III.

complete disappearance of all visible and palpable tumor.

Soluble Fractions

Figure 1 illustrates a representative curve of elution of the soluble preparations from Sephadex G-200. Fraction II gave the great majority of responses but occasionally fraction I and III produced a positive skin test.

There was less specificity seen when the soluble fractions were tested (Table 2). The autologous and allogeneic fractions prepared from mammary cancer, from normal tissue from the same breast as well as from normal breast of fibrocystic disease patients elicited almost identical reactions in mammary cancer patients. However, there was less reactivity to these soluble preparations in patients with other types of malignancy (Table 2). Comparing the results of the tests between the two cancer groups, 90% (9/10) of mammary cancer patients had positive reactions to soluble breast tumor fractions while 50% (2/4) of the other cancer group was positive to these tumor fractions. As can be seen in Table 2 the patients with either benign or malignant mammary disease also had a relatively high percentage of reactivity to both types of normal breast fractions (N-N breast and N-Ca breast) compared to patients with other diseases, benign or malignant, not related to the breast.

Discussion

Hughes and Lytton[18] reported that 27% (9/33) of patients with solid tumors gave a delayed hypersensitivity skin reaction to autologous tumor cell extracts but not to similar normal tissue. However, two patients reacted to both control and tumor tissues. Their preparations were thought to be free of cell membranes and consisted mainly of "smaller cytoplasmic particles" which are not particularly rich in transplantation antigens. Some of the extracts were treated with neomycin and 1500-300 μg. of "material" was injected intradermally. The above methods raise doubts as to whether the skin reactions were tumor specific since some of them may be related to antibiotic or antibiotic-bacterial complexes. We have also noted from previous studies, that the intradermal injection of more than 300 μg. of protein often gave a non-specific skin response.[2,19]

Stewart obtained results similar to Hughes and Lytton, employing extracts prepared by differential centrifugation.[22] He used extensive and ingenious methods to eliminate bacterial contamination as the cause of the skin reactions but this question still remains open. It was of interest that approximately 40% (6/17) of solid tumor patients gave a positive skin test to normal tissue adjacent to the tumor and a very small percentage to normal white cell extracts. There was no reaction to other types of control tissue (muscle). Stewart also tested mammary cancer patients with autologous tumor extracts.[21] As in his previous studies, Stewart could correlate the degree of round cell infiltration of the tumors with the patients' skin responses. However, there was essentially no correlation of skin reactivity with the stage of the disease. In addition patients with a delayed hypersensitivity skin reaction had a poorer survival rate than patients with negative skin tests. The latter result is different from most other similar studies and might be due to the time that the skin tests were carried out; some tests were performed within 4 days of operation when many patients are immuno-suppressed from the extent of the operative procedure.

TABLE 2. *Delayed Hypersensitivity Skin Reactions to Separated Soluble Membrane Fractions of Breast Tissues—(See Table 1 for explanations).*

	Soluble Fractions			
Type of patient	Ca Breast	N-Ca Breast	N-N Breast	Muscle-Mastectomy Specimen
Cancer				
Breast				
autologous	5/6	3/5	------	0/2
allogeneic	4/4	3/4	4/5	1/1
Other Cancer	2/4	1/4	1/4	ND

Benign Disease				
Breast	------	------	3/4	------
Other	------	------	0/3	------

Fass, Herberman and co-workers[9,19] have investigated the delayed hypersensitivity skin reactions to autologous membrane extracts from patients with Burkitt's lymphoma and acute leukemia. Sterile technics were employed and protein concentrations below 300 gamma were used. In these two studies, they were able to correlate positive skin tests with tumor remission.

Our results confirm the previous observations that breast tumor extracts both autologous and allogeneic, can elicit delayed hypersensitivity skin reactions in man. The reactions with the membrane preparations appeared to be tumor specific. However, the soluble membrane fractions gave less specificity. More mammary cancer patients responded to soluble fractions than did patients with other types of malignancies, but the mammary cancer patients were just as reactive to normal soluble breast fractions derived from either mastectomy specimens or from breast tissue of fibrocystic disease patients. This suggests that reactivity to an organ specific antigen is being detected in the soluble fractions. Further fractionation studies will be needed to determine whether a tumor specific antigen in the soluble mammary cancer extracts can be separated from the organ associated antigen.

The different pattern of reactivity produced by the soluble fractions as compared to the membranes is of considerable interest. It is possible that only the tumor associated antigen is recognizable on the membranes, and that the solubilization procedure uncovers the organ associated sites. Alternatively, the sonication could have induced changes in the membrane proteins, producing antigens to which many people have been sensitized.

Edynak and co-workers[8] and Priori *et al.*[20] have reported somewhat similar findings. Edynak using immuno-diffusion tests found that almost 50% (17/42) of mammary cancers from radical mastectomies contained a fetal antigen. The normal breast tissue from the operations (adjacent to or far removed from the primary tumor) had the same fetal antigen and so did three of five biopsies from the contralateral normal breast. In indirect immuno-fluorescent studies by Priori and co-workers, sera from patients with mammary cancer or fibrocystic disease were positive against monolayer cultures derived from mammary cancer, fibrocystic disease or osteo-sarcoma patients. Other cell lines were negative and normal sera were non-reactive. Chan *et al.*[5] using complement fixation also observed that 45% of sera from mammary cancer patients reacted to an antigen prepared from a mammary cancer cell line. Thirteen per cent of sera from patients with benign breast disease (fibrocystic and fibroadenomas) and 5 per cent of normal sera were also positive.

It is still disputed whether fibrocystic disease of the breast is pre-malignant. However, the above reports and our findings point to an immunological similarity between the breast with fibrocystic disease and the breast with malignant disease. Edynak interpreted the finding of a similar antigen in normal and tumor tissues as further evidence of the multicentric nature of mammary cancer and our findings would support the hypothesis that diffuse immunological changes can occur throughout the breast with cancer without phenotypic changes. This might be analogous to mouse mammary tumors where viral antigens can be detected long before neoplasia is observed[7] or to the studies of Weiss *et al.*[23] which showed that preneoplastic breast nodules and breast tumors in mice free of virus elicited similar immunogenic responses.

Although the tests with mammary cancer membranes appeared to be specific, the low frequency of positive responses under the conditions used appear to make diagnostic application unlikely. The patients with stage I and II mammary cancer have not been followed long enough to determine the prognostic significance of a positive or negative skin test. The results of the membrane skin tests in patients with stage III mammary cancer, although few in number, raise the possibilities that a positive reaction to tumor membranes is associated with a long tumor-free interval and that subsequent hormonal treatment may be beneficial. It has been difficult to actually identify the mammary cancer patient with a hormonal dependent tumor and the preliminary results noted would warrant further studies in this regard. The ability to diagnose or prognosticate the outcome of mammary cancer with skin tests using soluble fractions is not feasible at this time because of the reactivity of patients with benign breast disease. However, the biological implications could be significant. We are planning to continue these tests and relate them to *in vitro* assays of cellular immunity as well as to the clinical course of the patients. The question of immunogenicity of these extracts is also important from the standpoint of therapy and limited clinical trials are now underway.

Summary

Six of 13 patients with mammary cancer had a delayed hypersensitivity skin reaction to autologous and allogeneic mammary cancer membrane extracts but not to normal breast membranes derived from either the same mastectomy specimen or from breast tissue of patients with fibrocystic disease. Three of these patients had disseminated mammary cancer and their clinical course indicated that host responses were significant. Five patients with other types of malignancies did not react to any of these preparations. This suggests that a

common tumor associated membrane antigen is being detected in the mammary cancer patients.

Autologous or allogeneic solubilized fractions from mammary cancer membranes also elicited a delayed hypersensitivity skin reaction in a higher percentage of mammary cancer patients than in patients with other types of cancer. However, the soluble fractions derived from either normal breast of the mastectomy specimen or from fibrocystic disease were just as reactive in mammary cancer patients or patients with benign breast disease as the soluble tumor fractions. The significance of these cross-reactions in patients with benign or malignant breast disease is discussed.

Acknowledgments

We are grateful to O. B. Lee, J. Levy and M. Lichtenstein for excellent technical assistance.

This study was supported by USPHS 69-2176, National Institutes of Health.

References

1. Alford, C.: Disseminated Breast Cancer. Surg. Gynecol. Obstet., **117**:634, 1963.
2. Alford, C. and Hollinshead, A. C.: Unpublished Results.
3. Berg, J. W.: Morphological Evidence for Immune Responses to Breast Cancer. Cancer, **28**:1453, 1971.
4. Black, M. M. and Leis, H. P.: Cellular Responses to Autologous Breast Cancer Tissue. Correlation with Stage & Lymphoreticuloendothelial Reactivity. Cancer, 28:263, 1971.
5. Chan, S. P., Maca, R. D., Levine, P. H. and Ting, R. C.: Immunological Studies of Human Breast Cancer 1. Serum Reactivity against a Lymphoid Cell Line (Belev) derived from a Breast Cancer Patient as Detected by Complement Fixation Tests. J. Nat. Cancer Inst., 43:511, 1971.
6. Davies, D. A. K.: Mouse Histocompatability Isoantigens Derived from Normal and from Tumor Cells. Immunology, **11**:115, 1966.
7. Dmochowski, L.: Viruses and Breast Cancer. Introductory Remarks. Cancer, 28:1404, 1971.
8. Edynak, E. M., Lardis, M. P. and Vrana, M.: Antigenic Changes in Human Breast. Cancer, **28**:1457, 1971.
9. Fass, L., Heberman, R. B. and Ziegler, J.: Delayed Cutaneous Hypersensitivity Reactions to Autologous Extracts of Burkitt-Lymphoma Cells. N. Engl. J. Med., 282:776, 1970.
10. Hellstrom, I., Hellstrom, K. E., Pierce, G. E., and Yang, J. P. S.: Cellular and Humoral Immunity to Different Types of Human Neoplasms. Nature, **220**:1352, 1968.
11. Hellstrom, K. E. and Hellstrom, I.: Cellular Immunity Against Tumor Antigens. Adv. Cancer Res., **12**:167, 1969.
12. Hollinshead, A. and Alford, C.: Identification of a Soluble Transplantation Antigen from the Membrane Fraction of Adenovirus Tumor Cells. J. Gen. Virol., **5**:411, 1969.
13. Hughes, L. E. and Lytton, B.: Antigenic Properties of Human Tumors: Delayed Cutaneous Hypersensitivity Reactions. Br. Med. J., **1**:209, 1964.
14. Lowry, O. H., Rosenbrough, N. J., Farr, A. L.: Protein Measurement with the Folin Phenol Reagent. J. Biol. Chem., **193**:265, 1951.
15. Mann, D. L., Rogentine, G. N., Jr, and Fahey, J. S.: Solubulization of Human Leukocyte Membrane Isoantigens. Nature (London), **217**:1180, 1968.
16. Moore, D. H.: Search for a Human Breast Cancer Virus. Nature, **229**:611, 1971.
17. Moore, D. H., Larkar, N. H., Kramaorsky, B., Lasforgues, E. Y. and Charney, J.: Some Aspects of the Search for a Human Mammary Tumor Virus. Cancer, **28**:1415, 1971.
18. Old, L. J. and Boyse, E. A.: Immunology of Experimental Tumors. Ann. Rev. Med., **15**:167, 1964.
19. Oren, M. E. and Heberman, R.: Delayed Cutaneous Hypersensitivity Reactions to Membrane Extracts of Human Tumor Cells. Clin. Exp. Immunol., 9:45, 1971.
20. Priori, E. S., Seman, G. Dmochowski, L., Gallager, H. S. and Anderson, D. E.: Immuno-Fluorescence Studies on Sera of Patients with Breast Carcinoma. Cancer, **28**:1462, 1971.
21. Stewart, T. H. M. and Orizaga, M.: The Presence of Delayed Hypersensitivity Reactions in Patients toward Cellular Extracts of their Malignant Tumors. The Frequency, Duration and Cross-Reactivity of this Phenomenon in Patients with Breast Cancer and its Correlation with Survival. Cancer, **28**:1472, 1971.
22. Stewart, T. H. M.: The Presence of Delayed Hypersensitivity Reactions in Patients Toward Cellular Extracts of their Malignant Tumors. Cancer, **23**:1368, 1969.
23. Weiss, D., Sulitzeanu, A., Young, L., Adelberg, M. and Segev, Y.: Studies of the Immunogenicity of Preneoplastic and Neoplastic Mammary Tissues of Balb/c Mice Free of the Mammary Tumor Virus. Israel J. Med. Sci., **7**:187, 1971.

Axillary Metastases from Unknown Primary Sites

EDWARD M. COPELAND, M.D.,* CHARLES M. MCBRIDE, M.D.**

From the Department of Surgery, The University of Texas at Houston, M. D. Anderson Hospital and Tumor Institute, Houston, Texas 77025

CANCER, first detected by biopsy of an axillary mass, can be a perplexing diagnostic problem. Often a good history and physical examination will reveal the site of the primary lesion. All too frequently, however, examination of the gastrointestinal and genitourinary tracts, skin, thyroid, lungs, breast, or head and neck, fails to reveal a primary malignant neoplasm. Feuerman, Attie, and Rosenblum[1] reported the cases of 21 such patients in 1962. One third of these patients proved to have mammary cancer. We were interested in the follow-up of patients without proven mammary cancer.

Review of the records of the past 20 years at The University of Texas at Houston M. D. Anderson Hospital and Tumor Institute revealed 60 patients with axillary metastasis and no known primary site on initial evaluation. Each patient's work-up included a thorough history and physical examination (specifically oriented to the detection of skin cancer), full radiographic and diagnostic genitourinary and gastrointestinal studies, bone survey, chest X-ray film, thyroid evaluation, mammography, brain and liver scans when available, and complete head and neck examination. Nineteen of these patients, approximately one third, were subsequently treated for mammary cancer, of whom 18 instances were proved antemortem and reported separately by Westbrook and Gallager.[3] The 42 remaining patients (Table 1) are reviewed in this report in an attempt to formulate a plan of treatment for patients with axillary metastasis from an unknown primary site and to predict the fate of these patients.

Clinical Material

Epidemiologic data were of minimal prognostic value. Figure 1 shows the age distribution when axillary malignancy was first discovered. The youngest patient was 5 years old; the oldest was 82. Sex distribution was relatively even, 23 males and 19 females. Thirty-six of the patients were white and six black. All six Negro patients were female.

In 32 patients, a palpable mass was the only presenting symptom; it was usually discovered by the patient while bathing. In ten of the patients, both mass and pain were the presenting symptoms. The size of the lesion when the patient was first seen was variable, ranging from 1.5 cm. to 9 cm. in diameter. As for tumor site, 20 were initially noted in the right axilla and 22 in the left. Medical advice was usually sought between 8 and 24 weeks after initial detection of the mass; the range, however, was from 1 week to 1 year. In only three of the 42 patients was the organ of primary origin discovered antemortem. Thus the majority of these patients were followed throughout their life span without definite determination of the primary site.

Non-survivors in Whom Site of Origin was Undetermined

Twenty-four patients, in whom a definitive primary lesion was never found, died of the disease (Table 1). When initially evaluated, 12 of these patients had no evidence of metastasis other than in the axilla. The remaining 12 patients had other metastatic sites on first evaluation. Patients who initially had detectable metastasis in the axilla only survived a longer period of time. Their mean survival was 21 months as compared to 11 months for those with other metastatic foci. This difference did not appear to be a result of the latter group's reluctance to seek medical advice. The mean interval between onset of disease and treatment in the group with no other metastasis was 2.4 months as compared to 4 months for those with metastasis.

Eight of the 12 patients without other metastatic sites had axillary dissection following thorough evaluation. Positive nodes were identified in each case. In five patients more than one half of the recovered nodes contained tumor. In each instance, axillary dissection was performed for patients with unclassified malignancy but

---

Submitted for publication May 26, 1972.

TABLE 1. *Outcome of 60 Patients Initially Presenting with Axillary Metastasis from an Unknown Primary*

Diagnosed and treated as primary breast cancer		18
Dead with site of origin undetermined	24	
Dead with site of origin determined	9	
Survived with no evidence of disease	9	
	—	
	42	
		—
Total		60

TABLE 2. *Sites of Nonaxillary Metastasis*

Site	Nonaxillary Metastasis Detected at Initial Evaluation	Nonaxillary Metastasis Detected Subsequent to Initial Evaluation
Supraclavicular (ipsilateral)	3	3
Lung	7	5
Generalized dermal	1	4
Recurrent axillae	0	2
Brain	1	0

with elements suggestive of squamous cell carcinoma or amelanotic melanoma. Those patients with other metastatic foci had multiple forms of palliative therapy, including chemotherapy and radiotherapy. No definite evidence of disease regression could be identified.

In those 12 patients without evidence of disease outside the axilla, further metastasis occurred on an average within 14.5 months. After the axilla, the supraclavicular nodes were the next site of lymphatic drainage, but were not necessarily the next site of disease spread. The lung or dermal metastases were more likely sites (Table 2). Similarly, the site of further metastasis on initial evaluation at MDAH was the pulmonary parenchyma (Table 2).

Non-survivors in Whom Site of Origin was Determined

Nine patients had definitive primary diagnoses either from axillary biopsy or at postmortem (Tables 1 and 3). All nine are dead from the disease. Three of the patients were male, six female. The average age was 54 with a range between 43 and 72. In six of these patients the primary lesion was not found until postmortem examination. Local excision was the usual mode of surgical therapy and metastatic deposits other than in the axilla were rapidly discovered. In the patient with Hodgkin's disease, the breast was believed to be the primary site and was treated with comprehensive radiation. At postmortem, Hodgkin's disease was discovered. Three patients had mucin-producing adenocarcinomas, diagnosed on axillary biopsy, two of whom have subsequently died. At postmortem these two patients were found to have had primary stomach cancer which had not been obvious on clinical evaluation. The third patient underwent local axillary excision in 1967, which revealed mucin-producing adenocarcinoma. This evaluation and one in 1969 failed to reveal a primary site. The patient was given prophylactic 5-fluorouracil in 1969 and remained free of disease, although he is still on medication at last evaluation (Table 4).

Patients Surviving with No Evidence of Disease

Nine patients remained free of disease 2 to 10 years after initial diagnosis of a malignant lesion in the axilla (Tables 1 and 4). Two of these patients died of other causes 2 years after the initial discovery of the disease, and no evidence of residual malignancy was found at postmortem examination. In no instance was the primary origin of the malignancy located. Five of the patients were male, four female; seven were white and two black. The average age of the patients was 54, with a range between 43 and 72 years. The distribution of these figures is similar to that for the whole series. In two of these patients, axillary dissection was carried out because there was a suggestion of amelanotic melanoma. There was one positive node in one patient; none in the other. The other seven patients had local excision as the only form of surgical therapy.

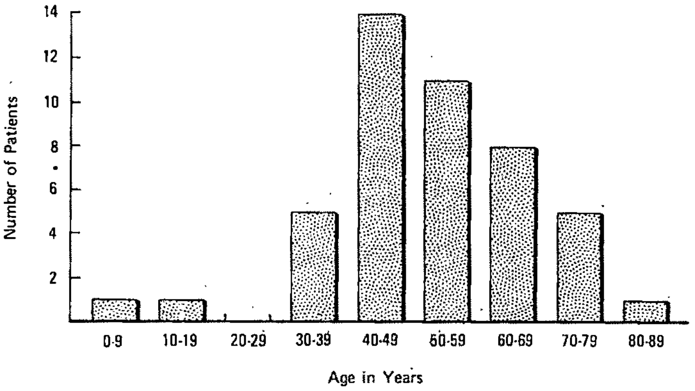


FIGURE 1

TABLE 3. *Summary of Patients with a Definitive Pathologic Diagnosis*

Diagnosis (One patient each)	Length of Life Following Axillary Diagnosis (months)	Mode of Surgical Therapy
Lung (Postmortem)	36	Axillary dissection (16/19 positive nodes)
Breast (Postmortem)	24	Local excision
Rhabdomyosarcoma	12	Local excision
Fibrosarcoma	8	Local excision
Stomach (Postmortem)	8	Local excision
Neurogenic sarcoma	6	Axillary dissection (12/18 positive nodes)
Stomach (Postmortem)	6	Local excision
Hodgkin's (Postmortem)	6	Local excision
Pharynx (Postmortem)	6	Local excision

Three of the surviving patients had undifferentiated metastases possibly from a primary lesion in the breast. Each patient received comprehensive radiotherapy and was free of disease 2 to 5 years post-therapy.

Table 5 lists the pathologic diagnoses of the axillary specimens removed from these nine patients as well as the 24 patients who died with no known primary site. The accuracy of the diagnosis of amelanotic melanoma or squamous cell components depended on the ability of the pathologist and more recently the use of electron microscopy. Nevertheless, the present survival for each group based on pathologic diagnosis was consistently 20 to 30 per cent (Table 5) with the exception of those with mucin-producing metastatic lesions. Those patients with a squamous element survived longer after diagnosis of the disease than did those in the other two groups.

TABLE 5. *Pathological Diagnosis of Axillary Mass in Patients with Primary Site Undetermined to Date*

	Total	Survivors (No Evidence of Disease)	Average Survival (Dead with Disease)
Poorly differentiated (Unclassified)	15	4	15.5 months
Poorly differentiated (Possibly amelanotic melanoma)	10	2	10 months
Poorly differentiated (Suggest squamous ca.)	7	2	30 months
Poorly differentiated (Mucin producing)	1	1	0 months

Conclusion

The physician must formulate an approach to treatment of axillary metastasis from an unknown primary site. Obviously all diagnostic methods to determine a primary source must be used. A thorough search of the skin of the extremity and trunk draining the ipsilateral axilla must be made. The possibility of a "disappearing" primary melanoma[2] or a small squamous cell lesion must be kept in mind. The patient should be questioned about previous skin lesions removed by electrocautery. Special staining technic and electron microscopy can be a great aid to the pathologist in diagnosing melanoma and various types of sarcomas.

In the experience of Feuerman, Attie, and Rosenberg,[1] once malignancy reached the axilla from an extramammary site, there were unequivocal signs pointing to the diseased organ of origin. This was true in very few of our patients. Nevertheless, we would agree with these authors and with Westbrook[3] that the breast is the most likely source of an undifferentiated axillary malignant lesion in women. In women with unclassified malignancies in whom no evidence of an extramammary source can be demonstrated, comprehensive radiotherapy to the ipsilateral breast and peripheral lymphatics would seem to be the treatment of choice. In those women with pendulous breasts or gross disease remaining in the axilla, a simple or extended simple mastectomy should be performed in order to make delivery of radiotherapy more efficacious. In women with small or atrophic breasts and minimal axillary disease, particularly those patients in whom no evidence of a breast primary can be demonstrated by mammography, xerography, or thermography, a mastectomy prior to radiation is not recommended. Radical mastectomies should not prove necessary.

TABLE 4. *Summary of Patients Free of Disease on Last Follow-up Evaluation*

Pathologic Diagnosis	Length of Life Following Diagnosis	Primary Mode of Therapy
Undifferentiated Suggest squamous ca.	10 yrs.	Local excision
Undifferentiated Suggest squamous ca.	8 yrs.	Local excision
Unclassified	5 yrs.	Local excision
Mucin producing adenocarcinoma	5 yrs.	5-FU
Unclassified	5 yrs.	Comprehensive XRT
Unclassified	2 yrs. (Dead, no evidence of malignancy)	Comprehensive XRT
Unclassified	2 yrs. (Dead, no evidence of malignancy)	Comprehensive XRT
Unclassified	2 yrs.	Axillary dissection (0/18 positive nodes)
Undifferentiated Suggest melanoma	2 yrs.	Axillary dissection (1/25 positive nodes)

Those patients with melanoma localized within the axillary lymph nodes should have an axillary dissection. The number of involved nodes can probably be used as a prognostic guide. Certainly those with more than five nodes involved have a poor prognosis. Men with unclassified malignancies should have axillary dissections for local control and, hopefully, for disease eradication. This also holds true for sarcomas localized within the axillary contents. Most patients with squamous cell lesions in this series were treated with local excision; squamous cell cancers tended to metastasize widely before recurring in the axilla. Experience with squamous cell metastasis to the axilla from known primaries, however, leads us to recommend axillary dissection for those with unknown primaries as well. These metastases if left alone, tend to become bulky and ulcerate, often requiring forequarter amputation for palliation alone. Needless to say, the patients require close follow-up study and proper therapy for the primary or metastatic disease as it becomes clinically apparent.

References

1. Feuerman, L., Attie, J. N. and Rosenberg, B.: Carcinoma in Axillary Lymph Nodes. Surg. Gynecol. & Obstet., **114**:5, 1962.
2. Smith, J. L. and Stehlin, J. S.: Spontaneous Regression of Primary Malignant Melanomas with Regional Metastases Cancer, **18**:1399, 1965.
3. Westbrook, K. C. and Gallager, S. H.: Breast Carcinoma Presenting as an Axillary Mass. Am. J. Surg., **122**:607, 1971.

Hartmann Procedure for Carcinoma of the Sigmoid and Rectum

ROBERT D. GONGAWARE, M.D.,* CHARLES A. SLANETZ, JR., M.D.**

From the Department of Surgery,
Presbyterian Hospital, New York City

REMOVAL OF THE SIGMOID COLON with intraperitoneal closure of the bowel below the tumor combined with an end sigmoid colostomy was first described by Henri Hartmann in 1921.[4] In 1927, his student, Soupault, reported on 31 cases with two operative deaths.[11] Hartmann reviewed his group of 34 cases in 1934.[5] In his series, there were four postoperative deaths resulting in an operative mortality of 8%.

The scope of Hartmann's operation was extended by Gabriel,[1] Rankin,[9] and Muir.[8] These surgeons used the operation for carcinomas at or below the peritoneal reflection, and left the closed rectal stump in an extraperitoneal position. Both Gabriel and Muir emphasized pelvic abscess as an important complication of the extended procedure. Golliger differentiated Hartmann's operation from "the Extended Hartmann Procedure."[3] Most surgeons, he believed, used the intraperitoneal operation. The major disadvantage cited by Golliger with the extended procedure was difficulty in establishing adequate drainage of the pelvic cavity when the rectal stump is closed in the extraperitoneal position.

This report represents a review of 100 consecutive Hartmann resections done at the Columbia-Presbyterian Medical Center and Francis Delafield Hospital from 1929–1969.

Clinical Study

Review of 100 consecutive Hartmann resections from 1929 through 1969 revealed that 61 were done after 1950. There were 56 men and 44 women in the series. The average age of the patients was 60.5 years (range 19 to 91 years).

Hartmann resection was employed as a palliative procedure in 65% of cases. Pathologic classification of tumors revealed 2% Duke's A, 26% Duke's B, 29% Duke's C, and 41 Duke's D (total 98%). Two procedures were done for gynecologic cancers. Extension of the carcinoma beyond the bowel wall was present in 43% and liver metastases were present in 27% of cases.

Hartmann's operation with intraperitoneal closure of the rectal stump was done in 43 instances. Extended Hartmann's procedure was done in 57 instances.

The indications for performing a Hartmann procedure are listed in Table 1. The procedure was chosen when anterior resection with anastomosis could not be safely accomplished and when the extended dissection of abdominoperineal resection was considered too hazardous. Often, when faced with sudden deterioration in the patient's condition during a planned anterior or abdominoperineal resection, the surgeon resorted to closure of the rectal stump and an end sigmoid colostomy to rapidly terminate the procedure. The presence of a perforated carcinoma with a pelvic abscess or locally extensive carcinoma suggesting inevitable local recurrence were also frequent indications.

Morbidity and Mortality

There were 18 hospital deaths resulting in a mortality rate of 18%. Thirteen of the patients died within 30 days of this operation. Pelvic abscess was the principal cause of death in 11 of the 18 hospital deaths. Three additional patients died of sepsis without pelvic abscess, one died of bronchopneumonia, one of pelvic hemorrhage, one of a thrombosed aorta and one of carcinomatosis. The breakdown of mortality according to type of procedure is noted in Table 2.

Postoperative pelvic infection was noted in 30% of cases with intraperitoneal closure of the rectal stump

---

Submitted for publication June 26, 1972.

[*] Chief Resident in Surgery, Presbyterian Hospital in New York City and Instructor in Surgery, Columbia University.

[**] Instructor in Surgery, Columbia University.

Address reprint requests to Robert D. Gongaware, M.D., 200 East 31st. Street, Savannah, Georgia 31401.

but was present in 75% of extended Hartmann procedures.

The average period of postoperative hospitalization for patients with intraperitoneal closure of the rectal stump was 25 days. Forty-two days were required for the extended Hartmann procedure. This longer period of hospitalization was directly related to the treatment of pelvic infection.

Long-term Follow-up

Of the 32 curative resections 10 patients, or 30% were free of tumor at 5 years. three patients had been lost to follow-up, and there were five operative deaths. The patients died of the disease an average of 31 months postoperatively.

Of the 69 palliative resections performed average survival was 11 months. Five patients in this group were lost to follow-up and one was alive at 42 months free of disease and one was alive at 31 months with recurrent disease.

Local recurrence rate for Duke's B tumors was 35% and was 48% for Duke's C tumors. This compares to a local recurrence rate of 25% for Duke's B and 38% for Duke's C following abdomino-perineal resection in cases reviewed at our institution from 1944 to 1963. During the same period, local recurrence following anterior resection was 23% for Duke's B and 33% for Duke's C cancers.[10]

Discussion

It is clear from our review that Hartmann procedures have been done at our institution primarily in the poor risk patient with advanced cancer in the hope of achieving an increased degree of palliation, in terms of longevity and comfort, over that available from colostomy alone.

The extended Hartmann procedure has been used frequently in poor risk cases where a low anastomosis was difficult and the prospect of local recurrence was high. In the recent 20-year period, 60 per cent of Hartmann resections involved extraperitoneal closure of the rectal stump whereas prior to 1950 less than half the cases were of the extended type.

Although mortality for the original type of Hartmann resection with intraperitoneal closure has declined from 30% to 9% as a result of improved preoperative preparation and postoperative management,[6] the extended Hartmann procedure still carries a 16% mortality. Despite antibiotic therapy, the extended Hartmann resection with its extraperitoneal closure of the rectal stump incurs a 75% incidence of pelvic septic complications and an average hospital stay of 42 days. Consider carefully this rate of morbidity in light of anticipated survival following palliative resection of cancer in the rectum or rectosigmoid. The average survival of less than 12 months in our series of extended Hartmann resections for incurable malignancy represents little significant palliation over simple diverting colostomy.[2]

TABLE 1. *Indications*

1.	Widespread metastases	18
2.	Locally extensive carcinoma	24
3.	Perforation with fecal spillage during surgery	9
4.	Preoperative perforation or abscess	9
5.	Technical difficulty with anastomosis	9
6.	Advanced age or "poor risk patient"	9
7.	Intraoperative physiologic emergency	6
8.	Indication not stated	16
	Total	100

If the extended Hartmann resection is to be used as an effective alternative to abdomino-perineal resection in poor risk patients, it is imperative that we reduce the risk of pelvic sepsis and mortality to more reasonable levels. Antibiotic preparation of the bowel and aseptic technic alone are not sufficient in the face of a contaminated retroperitoneal space between rectal stump and peritoneal closure. Adequate drainage of this space can best be accomplished by not closing the peritoneum at all, and by draining the pelvis with sump suction catheters either abdominally through a lower abdominal stab wound or behind the rectal stump in the presacral plane. Drainage through the rectal stump has proved unsatisfactory.

Although anterior resection, even with antibiotic preparation, carries a 12% risk of anastomotic or intrapelvic infections it is preferred to Hartmann resection if technically feasible.[10] When the patient is such a poor risk that abdomino-perineal resection is considered too hazardous, we might choose to perform a diverting colostomy and control the tumor by fulguration.[7,12] In cancer of the distal sigmoid where anastomosis is dangerous because of pelvic infection secondary to perforation of the tumor, unresectable spread within the pelvis, or intra-operative deterioration of the patient's condition we shall not hesitate to proceed expeditiously to a Hartmann type resection particularly where intraperitoneal closure with an adequate margin of resection is possible.

Summary

Hartmann's procedure for carcinoma of the pelvic colon is described and differentiated from extended

TABLE 2. *Mortality*

	1929–1950	1951–1969
Original Hartmann	7/20 = 35%	2/23 = 9%
Extended Hartmann	3/19 = 16%	6/38 = 16%

UNIVERSITY OF LIBRARY

Hartmann's procedure where the distal line of resection is extraperitoneal.

The original procedure has a definite but limited place in the surgeon's repertoire when dealing with a poor risk patient with carcinoma of the distal sigmoid. Extended Hartmann's procedure should be used only rarely and with caution. Methods of decreasing the mortality and morbidity of extended Hartmann's procedure are discussed.

References

1. Gabriel, W.: The Principles and Practice of Rectal Surgery. Charles C Thomas, Springfield, 5th Edition, p. 580.
2. Gabriel, W. B. and Lloyd-Davis, O. V.: Colostomy Br. J. Surg., **22**:520, 1935.
3. Golliger, J. D.: Surgery of the Anus, Rectum and Colon. Charles C Thomas, Springfield, 2nd Edition, 1967, p.625.
4. Hartmann, H.: 30th Congress Francais de Chirurgie—Process Verbeaux, Memoires, et Discussions, 30:411, 1921.
5. Hartmann, H.: Chirurgie du Rectum—Masson et Cie, Paris p. 344, 1931.
6. Herter, F. P. and Slanetz, C. A.: The Influence of Antibiotic Preparation of the Bowel and Complication After Colon Resection. Amer. J. Surg., **113**:165, 1967.
7. Madden, J. L. and Kandalaft, S.: Electrocoagulation, A Primary and Preferred Method of Treatment for Cancer of the Rectum. Ann. Surg., **166**:413, 1967.
8. Muir, E. G.: Abdominal Resection for Rectal Cancer. Lancet, **1**:1094, 1939.
9. Rankin, F. W.: The Technique of Anterior Resection of the Rectosigmoid. Surg. Gynecol. Obstet., **46**:537, 1929.
10. Slanetz, C. A., Grinnell, R. S. and Herter, F. P.: Comparison of Anterior and Abdomino-perineal Resection in the Management of Cancer of the Rectosigmoid. Am. J. Surg., **123**:110, 1972.
11. Soupault, R.: J. Chir. (Paris), **30**:513, 1927.
12. Strauss, A. A., Strauss, S. F., Crawford, R. A. and Strauss, H. A.: Surgical Diathermy of Carcinoma of the Rectum. JAMA, **104**:1480, 1935.

Leiomyoma of Meckel's Diverticulum— Preoperative Radiologic Demonstration

Case Report

IMAD F. TABRY, M.D., VICTOR H. NASSAR, M.D., JIRAYR P. BALIKIAN, M.D.

From the Departments of Pathology and Radiology,
The American University Medical Center,
Beirut, Lebanon

MECKEL'S DIVERTICULUM is known to occur in about two per cent of the general population[6] and becomes the site of pathologic changes in about 20 per cent of those individuals in whom it occurs.[10] Of the various pathologic entities involving this structure, neoplasms are a rarity occurring in about one per cent of the cases.[7,10] However, analysis of a series of 400 cases of Meckel's diverticulum did not mention a single case of neoplasm.[9] Reviewing the world literature and their own files, Weinstein *et al.*[11] could report 106 well documented cases of neoplasm of the Meckel's diverticulum in 1963; among these 26 were benign tumors and 80 were malignant. The most common benign tumor was leiomyoma of which 10 cases were reported. Since then we could find three new cases of leiomyoma in the more recent literature[2,4,5] making a total of 13 cases. In all the cases, however, the diagnosis was made at operation or were pathologic findings. The purpose of this paper is to report a case of leiomyoma of Meckel's diverticulum which was suspected preoperatively on roentgen examination and confirmed on pathologic study.

Case Report

A 65-year-old married Lebanese woman was admitted to A.U.M.C. because of recurrent episodes of rectal bleeding and chronic anemia of 4 years' duration. During these episodes she used to pass soft, dark stools, but no frank blood, pus or mucous. At no time did she have hematemesis. She also complained of heart burn for the past 40 years for which she was prescribed antacids and responded well. Several upper GI series failed, however, to demonstrate an ulcer. For the past 6 years she was hypertensive and her BP was controlled by Aldomet and Esidrix. The last episode of melena occurred 1 week prior to admission and lasted 3 days. On physical exam, BP was 130/70 mm. Hg, pulse 84 min, she looked very anemic. Her abdomen was soft, no mass was palpable on abdominal, rectal or vaginal examination. The rest of her physical examination was negative. Hematocrit was 18%, Guaiac tests repeatedly done on stools were negative during her stay in the hospital. TSP was 6.3 A/G:3.2/3.1, alkaline phosphatase, 3.4. She was transfused with 4 units of packed cells. Chest X-ray, barium enema and upper gastrointestinal series were negative. Small intestinal series showed an outpocketing measuring about 6 × 3 cm. in the ileum (Fig. 1). There was rigidity and thickening of its wall evidenced by failure of contraction of this outpocketing during fluoroscopic observation and increased distance between it and the adjacent bowel loops seen on subsequent films (Fig. 2). The inner wall was slightly irregular and at no time could any mucosal folds be demonstrated. In the lumen of this pouch, there was a small area of persistent filling defect, measuring about 1 cm. in diameter. The barium contrast was retained within the diverticulum as long as 8 hours, at which time all the barium from the small bowel was evacuated. The radiologic impression of the lesion was Meckel's diverticulum with an infiltrative process; neoplasm and chronic inflammation were considered.

At operation, a hard outpocketing was found at the anti-mesenteric side of the lower ileum, about 90 cm. proximal to the ileo-cecal valve. Large blood vessels passing to the anterior abdominal wall were stretched over the mass (Fig. 3). The mass was excised along with a 12 cm. segment of ileum, continuity being re-established by end-to-end anastomosis. There was no evidence of metastasis and the diagnosis was believed to be a tumor involving Meckel's diverticulum.

On gross pathology, the tumor was nodular on its surface, roughly spherical and measured approximately 6 cm. in diameter. On section, a central cavity was seen filled with watery fecal material and lined by an uneven dark granulation tissue. The cavity communicated with the intestine through an opening, measuring

---

Submitted for publication June 16, 1972.

Request reprints: Victor H. Nassar, M.D. Department of Pathology, American University Medical Center, Beirut, Lebanon.

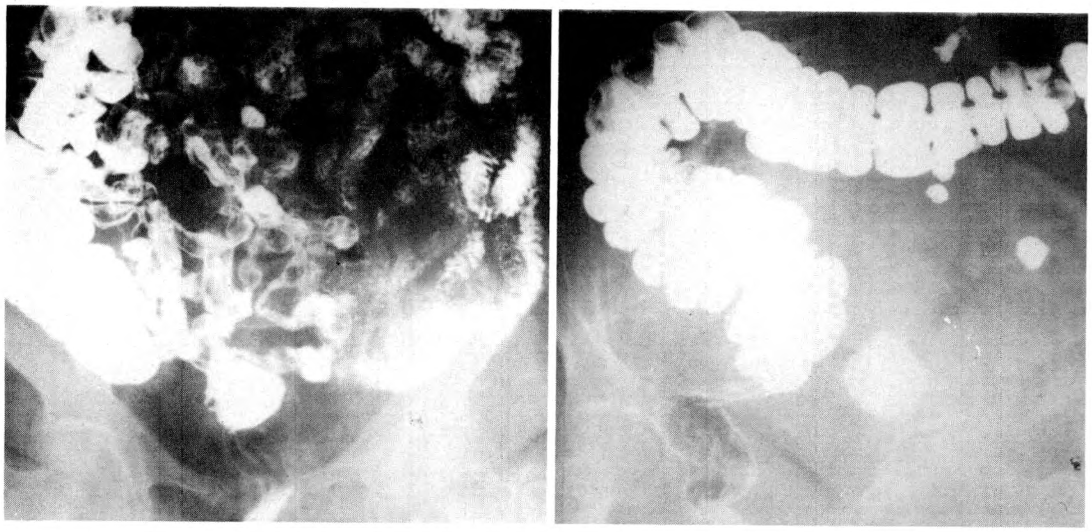


FIG. 1. A: (left) Small bowel series showing an outpocketing in the ileum. Note that the rest of the bowel appears normal. B: (right) delayed roentgenogram showing retention of barium in the diverticulum while there is complete evacuation from the rest of the bowel.

3 to 4 mm. in diameter. The wall of the tumor was thick and measured 1 to 2 cm. (Fig. 4). On cutting through it, several areas of calcification were recognized.

On microscopy, the solid part of the tumor was composed of interlaced bundles of closely packed spindle cells with large elongated oval nuclei. In some areas the cells formed a palisade arrangement (Fig. 5). The cellularity of the tumor was variable from area to area, being least in the calcified areas and highly cellular at places. However, mitotic figures were exceedingly rare. The tumor was not encapsulated and infiltrated the muscularis of the adjacent ileum. The mucosal side of the tumor was totally replaced by a layer of granulating tissue except on the edges where it was partly covered by intact intestinal mucosa (Fig. 6). The histologic diagnosis was: Cellular leiomyoma arising in the wall of Meckel's diverticulum.

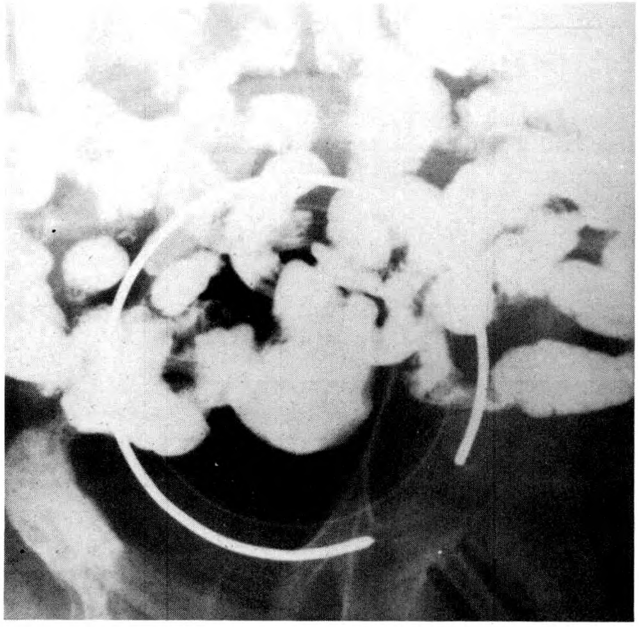


FIG. 2. Spot film made at fluoroscopy: the wall of the diverticulum was rigid and thickened with displacement of the surrounding bowel wall.

It is rare, if ever, that a tumor involving the Meckel's diverticulum, has been reported preoperatively. In this case, roentgenologic examination of the small intestine offered the clue to the diagnosis. In the Middle East, aneurysmal dilatation of the small intestine is frequently encountered in lymphomas of the gut.[1] However, in the latter, the dilatation is circumferential with loss of muscle tone and infiltration of the bowel wall with the lymphomatous process. This was not the situation in this case, since the lesion presented as an eccentric outpocketing.

At operation, the difficulty was to distinguish between a tumor arising in a Meckel's diverticulum and an eccentric leiomyoma[1] which perforated in the lumen of the intestine, a pseudo-diverticulum.[3,8] In this par-

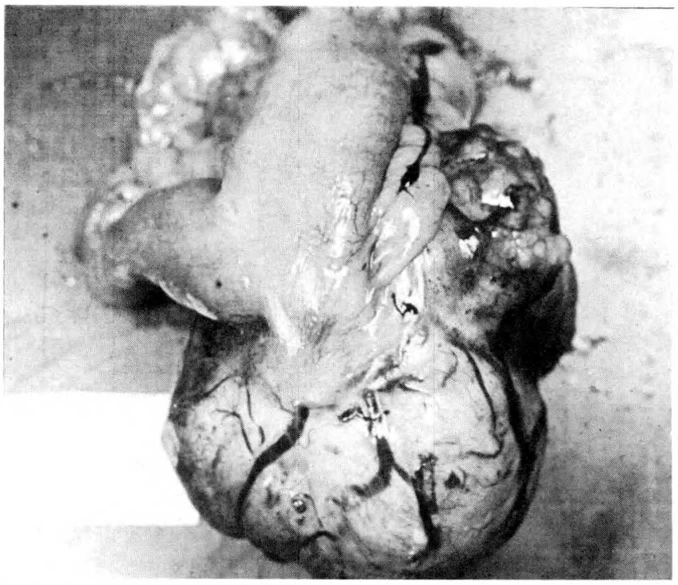


FIG. 3. Photograph showing enlarged remnants of the vitelline vessels stretched over the tumor.

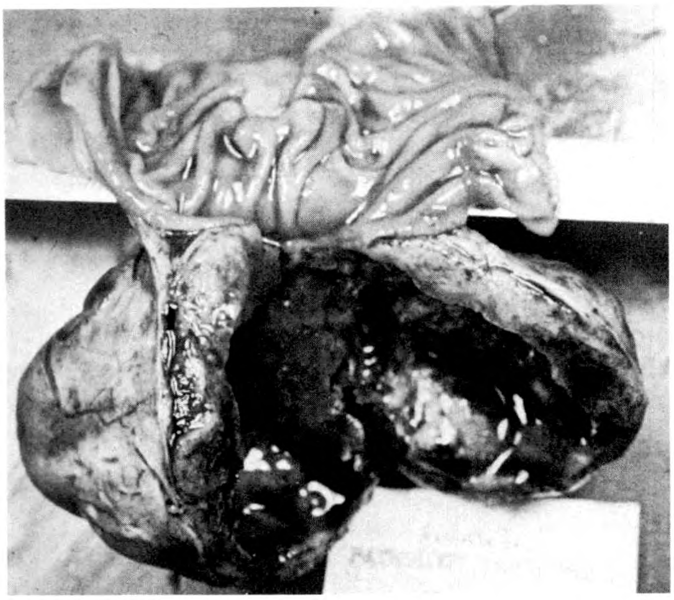


FIG. 4. Photograph showing cross-section of the tumor wall.

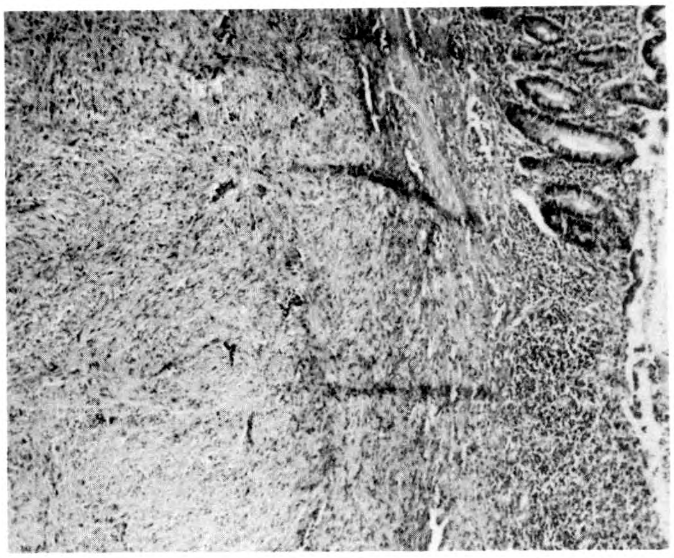


FIG. 6. A photomicrograph of the tumor shows the edges of the diverticulum covered with mucosa (×50; H.E.).

ticular case, the diagnostic value of enlarged remnants of the vitelline vessels was important in confirming the Meckelian origin of the tumor as supported by Weinstein *et al.*[11] Moreover, the edges of the tumor in our patient were covered by intact intestinal mucosa.

Histologically, the tumor was judged as a cellular leiomyoma, arising from the muscular coat of the intestine rather than a leiomyosarcoma; mitoses were rare.

Summary

Leiomyomas and leiomyosarcomas are the most common tumors of Meckel's diverticulum.[11] However, there is no record in the English literature of any correct preoperative diagnosis of tumor arising in Meckel's diverticulum even with the use of angiography.

A case of leiomyoma of Meckel's diverticulum is reported with a correct preoperative roentgen diagnosis. The detailed roentgenologic, operative and histologic findings are discussed.

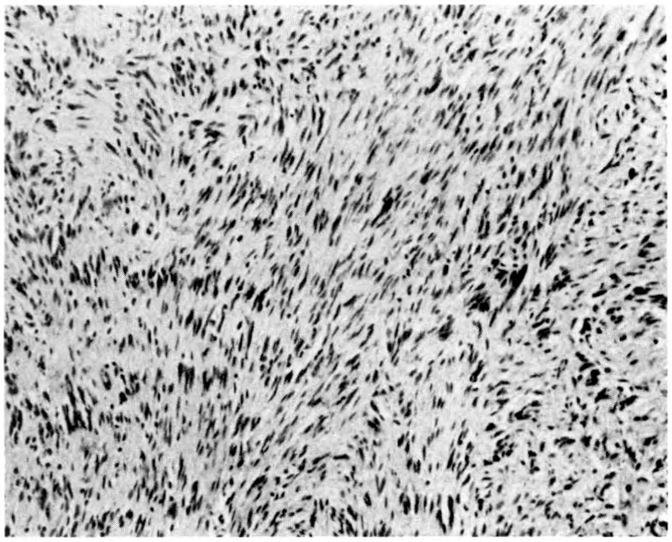


FIG. 5. A photomicrograph of the tumor shows detail of leiomyoma with palisading (×125; H.E.).

References

1. Balikian, J. P., *et al.*: Primary Lymphomas of the Small Intestine Including the Duodenum: A Roentgen Analysis of Twenty-nine Cases, Am. J. Roentgenol., **107**:131, 1969.
2. Garriz, R. A., *et al.*: Leiomyoma of Meckel's Diverticulum, Prensa. Med. Argent. **54**:123, 1967.
3. Golden, T. and Stout, A. P.: Smooth Muscle Tumors of the Gastrointestinal Tract and Retroperitoneal Tissues. Surg. Gynecol. Obst., **73**:784, 1941.
4. Kuipers, G., *et al.*: Leiomyoma and Meckel's Diverticulum as a Cause of Intestinal Hemorrhage, Zbl. Chir., **92**:2273, 1967.
5. Lombardi, A. R., *et al.*: Leiomyoma in Meckel's Diverticulum, Rass. Int. Clin. Ter., **50**:1104, 1970.
6. McParland, F. A. and Kieswetter, W. B.: Meckel's Diverticulum in Childhood, Surg. Gynecol. Obstet., **106**:11, 1958.
7. Moses, W. R.: Meckel's Diverticulum; Report of Two Unusual Cases, N. Engl. J. Med., **237**:118, 1947.
8. Starr, G. F., and Dockerty, M. B.: Leiomyomas and Leiomyosarcomas of the Small Intestine. Cancer, **8**:101, 1955.
9. Soderlund, S.: Meckel's Diverticulum; Clinical and Histologic Study, Acta Chir. Scand., Suppl. **248**:1, 1959.
10. Weinstein, E. C., Cain, J. C. and Remine, W. H.: Meckel's Diverticulum; 55 Years of Clinical and Surgical Experience, JAMA, **182**:251, 1962.
11. Weinstein, E. C., Dockerty, M. B. and Waugh, J. M.: Neoplasms of Meckel's Diverticulum: Collective Review. Int. Abstr. Surg., **116**:103, 1963.

Perforation of the Small Intestine Secondary to Laparoscopic Tubal Cauterization

EDWARD C. SALTZSTEIN, M.D.,* SAUL F. SCHWARTZ, M.D.**
CARL J. LEVINSON, M.D.*

From the Departments of Surgery and Obstetrics-Gynecology, Mount Sinai Medical Center, and the Medical College of Wisconsin, Milwaukee, Wisconsin 53233.

THE MOST SERIOUS COMPLICATION of laparoscopic tubal cauterization is unrecognized or inadvertent fulguration of the ileum.[2]

This paper reports three recent cases of perforation of the small intestine secondary to laparoscopic tubal cauterization. Although small intestinal burn has been mentioned as a possible complication of tubal fulguration,[2,3] we are unaware of specific case reports of small intestinal perforation in the literature.

Case Reports

Case 1. A 24-year-old woman, Gravida 3, Para 2, underwent laparoscopy with bilateral tubal fulguration on 10/5/71 (Mount Sinai Medical Center, Milwaukee, Wisconsin). Laparoscopic abdominal exploration was negative and tubal ligation was performed without incident utilizing the biopsy tong. The patient had a low grade fever the day following the procedure and complained of a slight sore throat, but 2 days after operation was afebrile and was discharged from the hospital.

On 10/8/71, 3 days after tubal ligation, the patient was readmitted to the hospital following sudden onset of lower abdominal pain starting with a cramp and becoming increasingly severe within one-half hour. She took a shot of brandy and vomited once after that. The pain described was not crampy in nature.

On physical examination, the abdomen was soft in the upper quadrants, but there was marked guarding in the lower quadrants. There was marked tenderness with rebound tenderness present in both lower quadrants. Rebound tenderness to a lesser degree was also present in the upper quadrants. The bowel sounds were hypoactive and slightly high pitched. Pelvic examination revealed marked paracervical tenderness. The white blood count on admission was 20,000 with a shift to the left. A low grade fever was present. X-rays revealed a minimal amount of gas without any free air present.

The impression at the time was that the patient had a complication of laparoscopic tubal ligation. The possibility of a burn with perforation of the small intestine was primarily considered, although pelvic inflammatory disease secondary to the surgical procedure was also considered. The patient was operated upon the evening of 10/8/71. A peri-umbilical midline incision was used. Upon entering the peritoneal cavity a moderate amount of murky peritoneal fluid was encountered. There were filmy and fibrous adhesions of the small intestine and pelvis to adjacent viscera. The uterus and tubes were inspected, and there was no evidence of acute inflammatory reaction. The site of tubal cauterization was identified and appeared to be normal for this state of postoperative recovery. A normal appendix was located in a retroperitoneal position. In the proximal ileum an area of perforation with localized coagulation necrosis about the perforation was identified (Fig. 1). The remaining small intestine was essentially normal.

An area of approximately 2 cm. surrounded the perforation which appeared to represent burned tissue. It was elected, therefore, to resect a 3 to 4-inch segment of small intestine to include all areas of coagulation necrosis. The patient made an uneventful recovery and was discharged from the hospital 9 days after operation.

Case 2. A 23-year-old Gravida 2, Para 2, woman was admitted to the hospital on 12/2/71 for an elective permanent sterilization procedure (St. Luke's Episcopal Hospital, Houston, Texas). On 12/3/71 a laparoscopy and bilateral tubal fulguration and division was performed, using the biopsy tong and the technic of coagulation followed by cutting/twisting. There were no unusual circumstances, and the intestine appeared to be well away from the coagulation site. However, in coagulating the left tube, "there was a blanching of the entire tube out to the fimbriated end." The patient had an uneventful postoperative course, and was dismissed from the hospital on the following day.

She was readmitted to the hospital on 12/10/71, following sudden onset of lower abdominal pain of a spurting diffuse nature. There was no nausea or vomiting. Abdominal examination revealed diffuse tenderness with moderate distention of the lower abdomen. The tenderness was most marked in the right lower quadrant. On pelvic examination, no abnormalities were noted. A culdocentesis returned 10 cc. of straw-colored fluid. The patient was treated

---

Submitted for publication July 13, 1972.

* Department of Surgery.

** Department of Obstetrics-Gynecology.

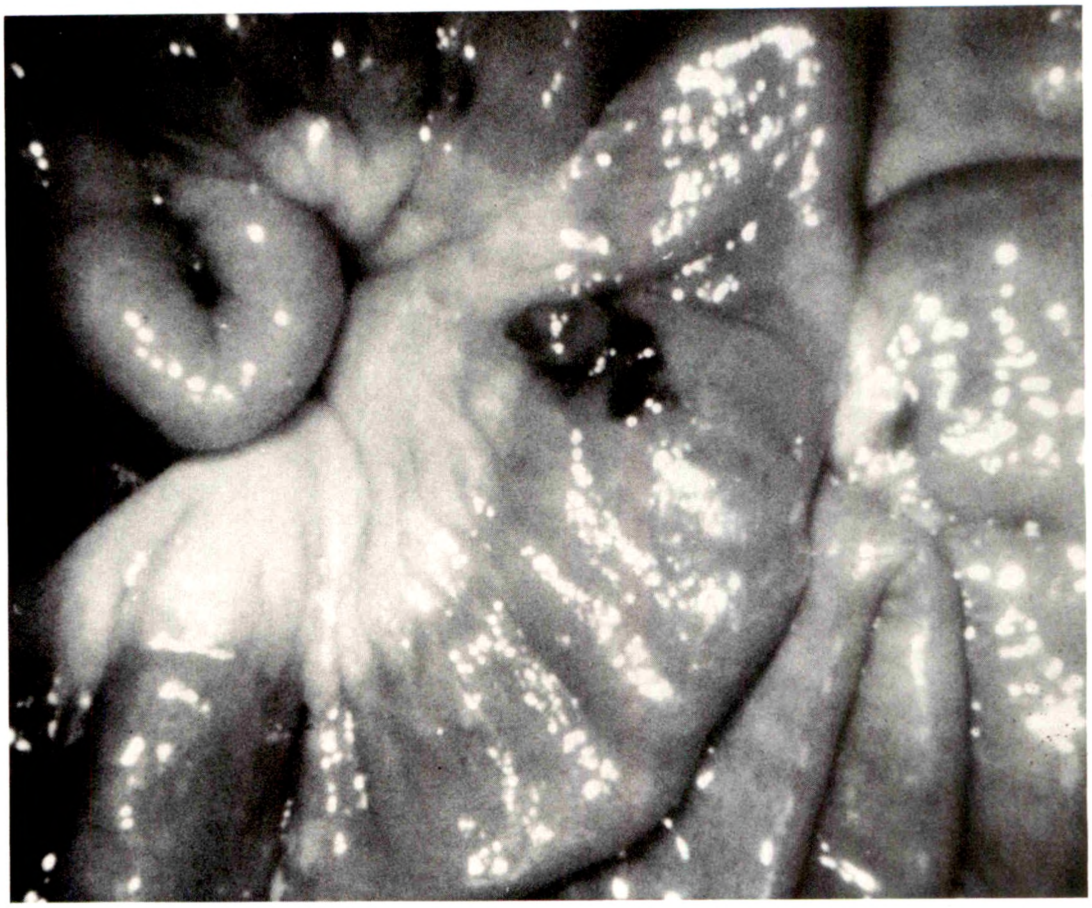


FIG. 1. Perforation of the distal ileum with surrounding burn reaction.

by intravenous fluids and medication for pain, and appeared to improve. However, she developed a temperature of 37.8 C, and the white count was elevated to 12,200 with a shift to the left, and the pulse rate increased. By 12/13/71, although the patient began to have intestinal function, the abdomen was distended and abdominal X-rays revealed loops of distended small intestine. Therefore, an exploratory laparotomy was performed, and a perforation of the distal ileum with a localized area of necrosis surrounding the perforation was identified. A resection of approximately 6 inches of ileum encompassing the perforation was performed. The postoperative course was uneventful.

Case 3. A 39-year-old woman, Gravida 3, Para 3, with a past history of cholecystectomy and pelvic surgery for endometriosis, underwent elective laparoscopy and bilateral electrocauterization and electro-surgical resection of the fallopian tubes on 10/13/70 (Doctors Hospital Complex, Milwaukee, Wisconsin). At operation, both fallopian tubes and ovaries were within normal limits.

Cauterization was performed with the biopsy tong. It was seen, after the second tube was cauterized and resected, that a section of approximately 1.5 cm. in greatest diameter of the small intestine had been cauterized. The area was white. The surrounding area was pink, and did not involve the mesentery of the small intestine. It was elected to observe the patient for possible intestinal problems.

Over the ensuing 36 hours there were increasing signs of peritoneal irritation and small intestinal obstruction, and the patient was operated upon the evening of 1/14/71. There was gross contamination in the right lower quadrant, and a loop of intestine was identified which was perforated. There was a great deal of burn reaction around the perforation. It was felt that closing the perforation would be unsatisfactory, and 6 to 8 inches of small intestine were resected. The patient made an uneventful recovery.

Discussion

The use of electrocoagulation to interrupt the integrity of the fallopian tube during laparoscopy is standard procedure. Reported complications of laparoscopic tubal cauterization are unusual, postoperative discomfort is minimal, and patients usually return to their normal activities within 24–48 hours.[1–7]

Coagulation necrosis of adjacent viscera by direct application of cautery or from sparking is a possible, even if extremely unlikely, complication of the proce-

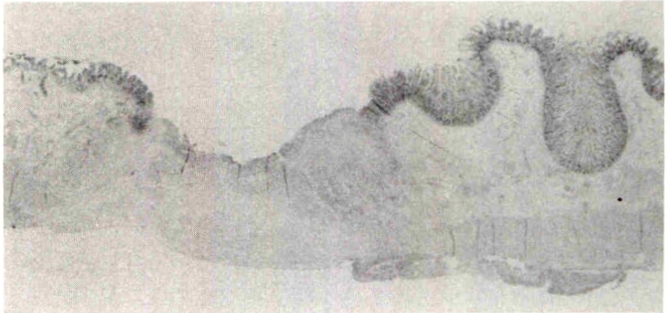


FIG. 2. Photomicrograph of the distal ileum showing extensive coagulation necrosis.

dure. In the first two cases reported above, the operating gynecologist had no difficulty in distending the abdomen, there were no adhesions, there was no intestine in the immediate area of the tube during cauterization, and the cautery was not inadvertently applied. In the third case, coagulation of the intestine was noted at the time of tubal cauterization. Although the patient had previous pelvic surgery for endometriosis, which could be expected to result in adhesions complicating the performance of laparoscopy, the tubes and ovaries were reported as easily visualized.

Steps to prevent coagulation necrosis of the small intestine are of extreme importance.[3–7] Proper equipment, and good anesthesia to avoid straining, are essential. Steep Trendelenberg and adequate gas distention of the abdomen as well as appropriate manipulation of the tube with the cauterizing instrument are measures to employ to avoid contact with adjacent intestine. The cautery attachment should be connected only during actual cauterization.

The clinical picture in the above reported cases suggests a typical pattern, consistent in all respects with spreading pelvic peritonitis. The first two patients had very uneventful postoperative recoveries from laparoscopic tubal cauterization until the third to seventh day when they developed sudden lower abdominal pain which began to spread to the remainder of the abdomen. This was associated with a rising fever and white count. Nausea and vomiting were inconstant accompanying symptoms. Physical examination revealed the presence of abdominal tenderness with rebound primarily in the lower abdomen. Pelvic examination was unremarkable except for evidence of peritoneal irritation. In both cases a complication of laparoscopy was suspected, and a differential diagnosis between postoperative pelvic inflammatory disease and small intestinal perforation secondary to electro-coagulation was made.

In the third case, intestinal burn was noted at the time of tubal cauterization, and perforation undoubtedly followed soon thereafter. Perforation in these three cases occurred hours, 3 days, and 7 days following intestinal burn, and the time delay from burn to perforation would appear to be related to the severity of the coagulation necrosis.

At operation, the small intestinal perforations were readily demonstrated. The degree of peritonitis depended upon the amount of spillage and the length of time from perforation to exploration. The small perforation, in all three instances, was surrounded by an area of coagulation necrosis grossly visible, and it was deemed advisable to resect a portion of small intestine sufficient to include this area of coagulation necrosis (rather than simple closure of the perforation). Histologic examination of the resected tissue confirmed the presence of coagulation necrosis spreading for 1–2 cm, (Fig. 2). Therefore, resection of small intestine would seem to be indicated to prevent subsequent reperforation, and resection of the small intestine with end-to-end anastomosis was followed by complete recovery in all three patients.

Exploration was delayed in Case 2. A trial of conservative therapy to treat a possible inflammatory process in the absence of a definite diagnosis of small intestinal perforation was deemed advisable. Delay in operation following intestinal perforation is fraught with complications, and further delay in operating on Case 2 could have had a high morbidity rate with secondary small intestinal obstruction and intra-abdominal abscess. Appropriate therapy appears to be immediate operation upon suspicion of small intestinal perforation. The risk of delay with perforation would greatly outweigh the risk of exploration for pelvic inflammatory disease in an otherwise normal young woman.

Summary

Three cases of perforation of the small intestine following laparoscopic tubal cauterization for female sterilization are reported. Measures to avoid cauterization of adjacent viscera during laparoscopy are emphasized. Patients have (unless perforation is immediate) sudden lower abdominal pain up to 7 days after tubal cauterization, and subsequently develop spreading peritonitis. The time delay from burn to perforation appears to be related to the severity of the coagulation necrosis. Appropriate treatment consists of prompt surgical exploration with resection of small intestine to include areas of coagulation necrosis surrounding the small perforation.

Acknowledgment

Case 2 was kindly forwarded to us by Dr. Raymond H. Kaufman, Acting Chairman, Department of Obstetrics-Gynecology, Baylor University College of Medicine.

Case 3 was kindly forwarded to us by Dr. Nathan M. Hilrich, Attending Gynecologist, Doctors Hospital Complex, Milwaukee, Wisconsin.

References

1. Black, W. P.: Sterilization by Laparoscopic Tubal Electrocoagulation: An Assessment. Am. J. Obstet. Gynecol., **111**: 979, 1971.
2. Black, W. P.: Sterilization by Laparoscopic Tubal Electrocoagulation: An Assessment. Obstet. Gynecol. Surv., **27**:383, 1972.
3. Corson, S. L. and Bolognese, R. J.: Laparoscopic Nuances. Fertil. Steril., **22**:684, 1971.
4. Fear, R. E.: Laparoscopy: A Valuable Aid in Gynecologic Diagnosis. Obstet. Gynecol., **31**:297, 1968.
5. Horwitz, S. T.: Laparoscopy in Gynecology. Obstet. Gynecol. Surv., **27**:1, 1972.
6. Peterson, E. P. and Behrman, S. J.: Laparoscopic Tubal Sterilization. Am. J. Obstet. Gynecol., **110**:24, 1971.
7. Seigler, A. M.: Trends in Laparoscopy. Am. J. Obstet. Gynecol., **109**:794, 1971.

- fights skin infections due to susceptible organisms
- rarely sensitizes

POLYSPORIN® OINTMENT

(polymyxin B-bacitracin)

Each gram contains: Aerosporin® brand Polymyxin B Sulfate 10,000 units; Zinc Bacitracin 500 units, in special white petrolatum q.s.

For minor burns, cuts, infections. Topical antibacterial action against a wide range of susceptible organisms. Rare chance of sensitization. Especially for patients with possible sensitivity to other topical antibiotics.

Available in 1- and ½-oz. tubes.

Contraindications: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components.

Caution: As with other antibiotic products, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

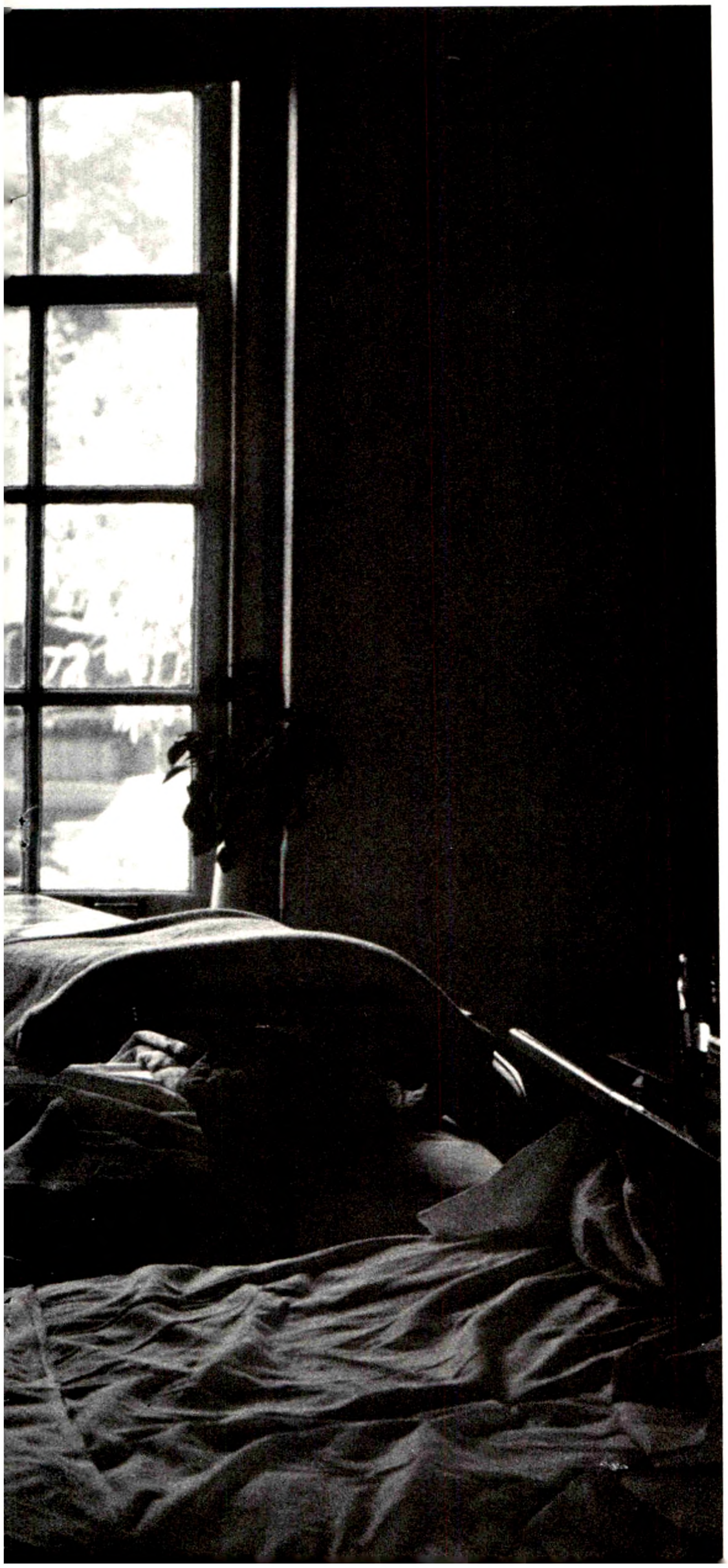
Complete literature available on request from Professional Services Dept. PML.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

when pain goes on...

nd on... and on–



For the patient with a terminal illness, PAIN past, present, and future can dominate his thoughts until it becomes almost an obsession. The more he is aware of the pain he is now experiencing, the more difficult it is to erase his memory of yesterday's pain, and to allay his fearful anticipation of tomorrow's pain.

Surely the last thing this patient needs is an analgesic containing caffeine to stimulate the senses and heighten pain awareness. A far more logical choice is Phenaphen with Codeine. The sensible formula provides ¼ grain of phenobarbital to take the nervous "edge" off, so the rest of the formula can help control the pain more effectively. Don't you agree, Doctor, that psychic distress is an important factor in most of your terminal and long-term convalescent patients?

the analgesic formula that calms instead of caffeinates

Phenaphen® with Codeine

Phenaphen with Codeine No. 2, 3, or 4 contains: Phenobarbital (¼ gr.), 16.2 mg. (warning: may be habit forming); Aspirin (2½ gr.), 162.0 mg.; Phenacetin (3 gr.), 194.0 mg.; Codeine phosphate, ¼ gr. (No. 2), ½ gr. (No. 3) or 1 gr. (No. 4) (warning: may be habit forming).

Indications: Provides relief in severer grades of pain, on low codeine dosage, with minimal possibility of side effects. Its use frequently makes unnecessary the use of addicting narcotics. **Contraindications:** Hypersensitivity to any of the components. **Precautions:** As with all phenacetin-containing products, excessive or prolonged use should be avoided. **Side effects:** Side effects are uncommon, although nausea, constipation and drowsiness may occur. **Dosage:** Phenaphen No. 2 and No. 3—1 or 2 capsules every 3 to 4 hours as needed; Phenaphen No. 4—1 capsule every 3 to 4 hours as needed. For further details see product literature.

CIII Phenaphen with Codeine is now classified in Schedule III, Controlled Substances Act of 1970. Available on written or oral prescription and may be refilled 5 times within 6 months, unless restricted by state law.

A. H. Robins Company, Richmond, Va. A·H·ROBINS

Injectable Valium® (diazepam) the versatile psychotherapeutic agent

prior to surgery

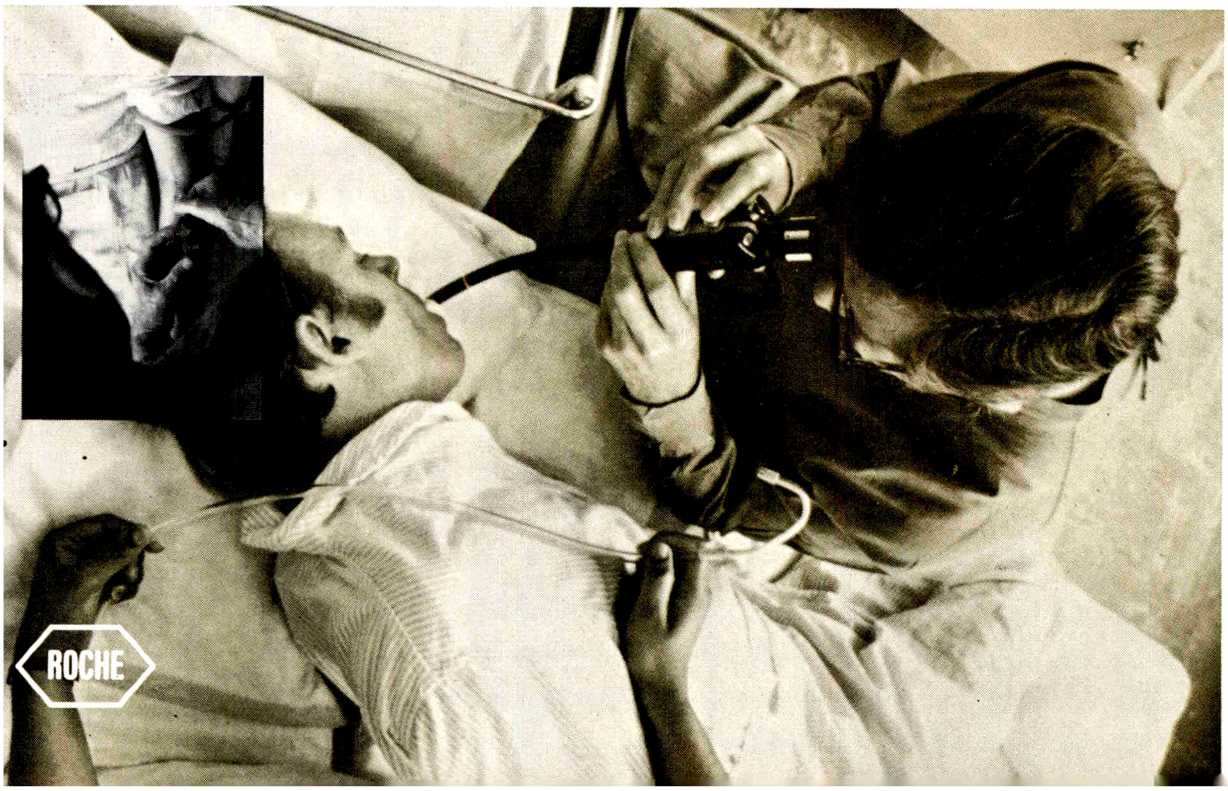
Injectable Valium (diazepam) can promptly calm the surgical patient by lessening the excessive anxiety and undue tension that may be associated with strange surroundings and disturbing procedures. And it can provide the added advantage of diminishing recall of preoperative procedures.

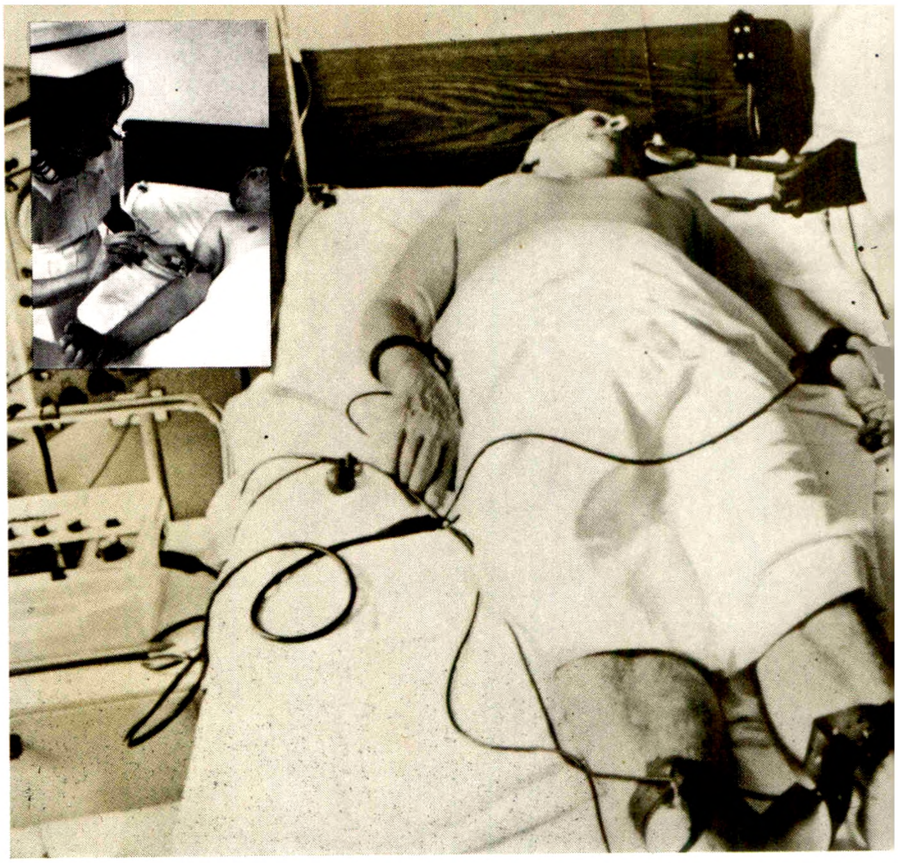
The recommended dosage is 10 mg, I.M., administered one to two hours preoperatively. Injectable Valium (diazepam) should not be mixed or diluted with other drugs, solutions or fluids.

adjunctively prior to gastroscopy and esophagoscopy

Injectable Valium (diazepam) can be a valuable adjunct in allaying excessive anxiety when it accompanies such procedures. It reduces the anxiety, yet allows the patient to cooperate by responding to commands and following instructions. It is not recommended for bronchoscopy and laryngoscopy because of the possibility of increased cough reflex and laryngospasm. Necessary countermeasures should be immediately available.

Half an hour before gastroscopy or esophagoscopy, a 5 to 10 mg dose is administered I.M. or I.V.





prior to cardioversion

Through relief of undue anxiety and excessive tension, Injectable Valium (diazepam) can effectively calm the patient. Memory of the cardioversion procedure can be markedly diminished. Injectable Valium seldom significantly alters vital signs. Nevertheless, there have been infrequent reports of hypotension and rare reports of apnea and cardiac arrest. Resuscitative facilities should be immediately available.

Five to ten minutes before elective cardioversion, the recommended dosage is 5 to 15 mg, injected slowly I.V. (5 mg/min.).

Injectable Valium® (diazepam)

ready-to-use 2-ml
Tel-E-Ject™
(disposable syringes)
10-ml vials
2-ml ampuls

} 5 mg/ml

For a summary of product information, please see the following page.

Injectable Valium® (diazepam)

the versatile psychotherapeutic agent

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus and severe recurrent seizures; anxiety prior to gastroscopy, esophagoscopy, and surgical procedures; cardioversion (I.V.).

Contraindicated: In infants; in patients with known hypersensitivity to the drug; in acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *Inject I.V. slowly, directly into vein; take at least one minute for each 5 mg (1 ml) given. Do not mix or dilute with other solutions or drugs. Do not add to I.V. fluids.* Rare reports of apnea or cardiac arrest noted, usually following I.V. administration, especially in elderly or very ill and those with limited pulmonary reserve; duration is brief; resuscitative facilities should be available. Not recommended as sole treatment for psychotic or severely depressed patients. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. Caution against hazardous occupations requiring complete mental alertness. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard to mother and child.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Not recommended for bronchoscopy, laryngoscopy, obstetrical use, or in diagnostic procedures other than gastroscopy and esophagoscopy. Laryngospasm and increased cough reflex are possible during gastroscopy; necessary countermeasures should be available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Since effect with narcotics may be additive, appropriate reduction in narcotic dosage is possible. Use lower doses (2 to 5 mg) for elderly and debilitated. Safety and efficacy in children under 12 not established.

Side Effects: Drowsiness, fatigue, ataxia, confusion, depression, constipation, dysarthria, diplopia, headache, hypoactivity, hiccups, hypotension, incontinence, jaundice, nausea, changes in libido, changes in salivation, phlebitis at injection site, urinary retention, skin rash, syncope, slurred speech, urticaria, tremor, vertigo, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial adult dose is 2 to 10 mg I.M. or I.V., depending on indication for use. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Precautions and Adverse Reactions.) In gastroscopy and esophagoscopy, 5 to 10 mg, I.M. or I.V., 30 min. prior to procedure. As preoperative medication, 10 mg, I.M., 1 to 2 hours before surgery. In cardioversion, 5 to 15 mg, I.V., within 5 to 10 min. prior to procedure. Give I.V. injections slowly; take at least 1 minute for each 5 mg (1 ml).

In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory; not more than 30 mg should be given within 8-hour period. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Supplied: Valium® (diazepam) Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject™ (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

ROCHE

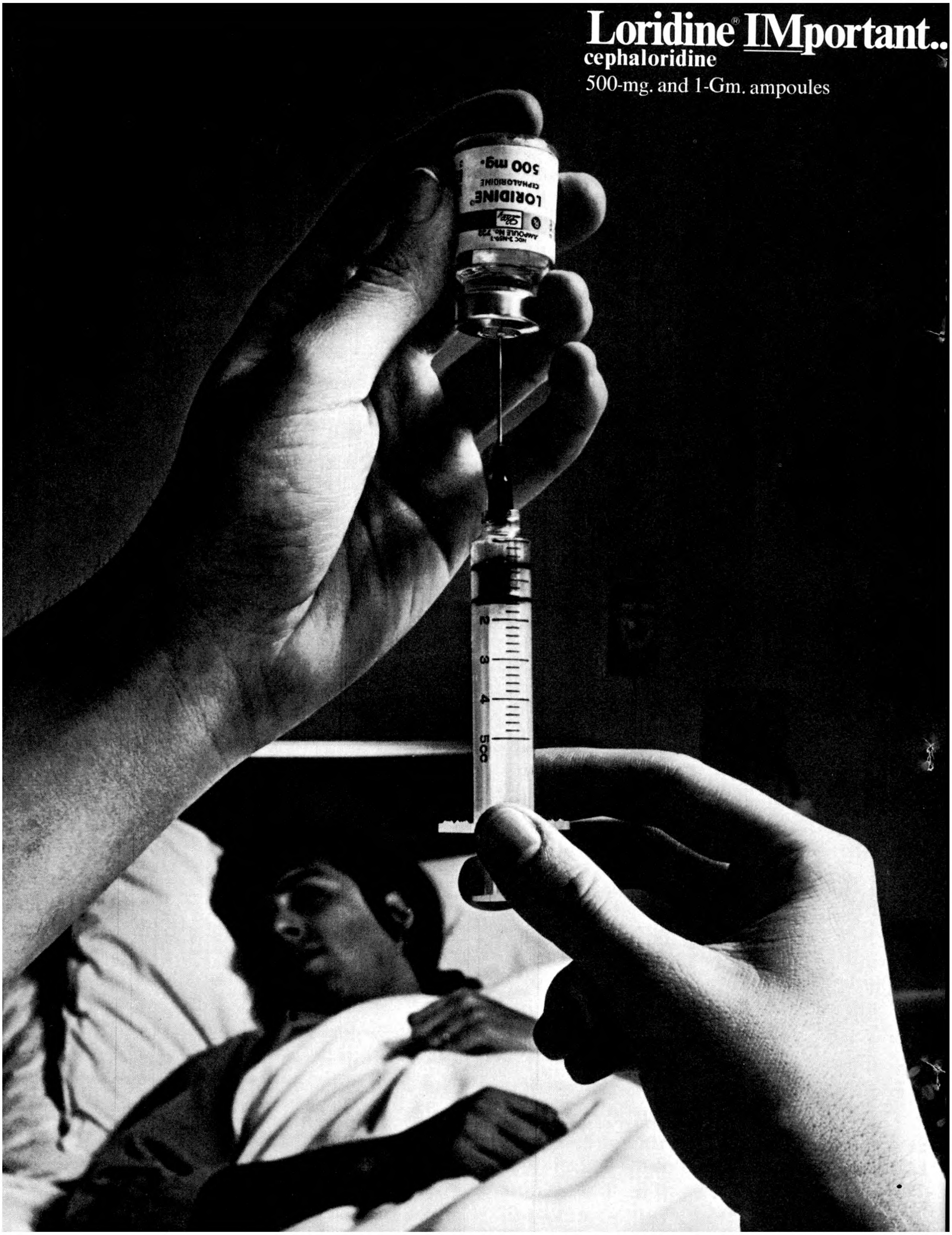
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

The Burdick Compact Coronary Care Center

—a sensible and economical answer to the hospital's need for coronary care facilities

The Burdick **Compact Coronary Care Center** answers the three demands of sound operational economy — **Mobility, Versatility** and **Full Utilization**—without equipment overpurchase. Specialized personnel and modern electronic monitoring equipment must be on constant 24-hour standby. Burdick's flexible approach will give you maximum versatility of equipment between departments. Start with the basic console ECG, adding equipment tailored to your need to extend your coronary care skills to a number of critical areas—one-bed ICU, mobile emergency room, stress-exercise monitoring, monitoring in Surgery and Recovery. Build to the complete mobile coronary care center for best utilization of both staff and equipment. For full information talk with your Burdick dealer, or write **The Burdick Corporation, Milton, Wisconsin 53563.**

BURDICK®


Loridine® IMportant..
cephaloridine
500-mg. and 1-Gm. ampoules
500 mg.
LORIDINE®
CEPHALORIDINE

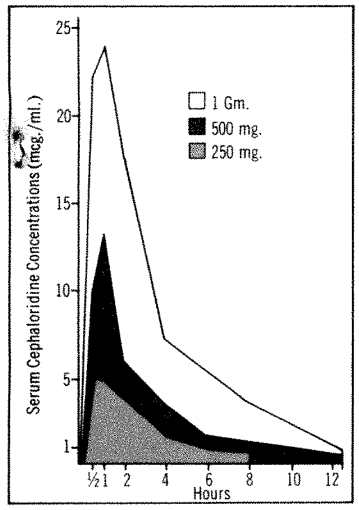
before the infection* goes any further

proved effective when susceptible organisms cause

pneumonia
bronchopneumonia
lobar pneumonia
bronchitis
empyema
cystitis
urethritis
prostatitis
pyelonephritis
pelvic inflammatory disease
wound infection
sepsis

produces prompt serum levels after I.M. administration

Doses of 500 mg. or 1 Gm. produce measurable serum levels up to twelve hours



Mean Serum Cephaloridine Concentrations after I.M. Administration of Single Doses (250 mg. to 1 Gm.) to Normal Human Volunteers (Six to Eighteen Subjects per Group) (modified from Currie, J.P.: Cephaloridine: Pharmacology and Toxicology, *Postgrad. Med. J., 43* [Supplement]: 22, 1967).

bactericidal in vitro against many commonly encountered gram-negative and gram-positive organisms

In-vitro sensitivity of selected micro-organisms (cumulative percent of isolates inhibited in broth and agar-dilution studies†)

Gram-Negative Micro-Organisms	MIC (mcg./ml.)						
	0.12	0.5	1.5-2	3.12-4	6.25-8	12.5-16	25-32
Hemophilus influenzae, 235 isolates	5.1	8.1	20.4	38.3	60.4	76.2	93.2
Escherichia coli, 1,424 isolates	—	1.1	33.4	65.2	83.1	90.2	92.8
Proteus mirabilis, 519 isolates	—	—	1.3	8.1	40.5	65.9	79
Klebsiella sp., 527 isolates	—	—	6.6	53.7	75.5	86.3	89.6
Klebsiella-Enterobacter, 372 isolates	—	—	52.2	65.1	72	82.3	84.7
Neisseria gonorrhoeae, 747 isolates	—	1.2	36	44.2	81.9	99	—

Gram-Positive Micro-Organisms	MIC (mcg./ml.)						
	0.12	0.5	1.5-2	3.12-4	6.25-8	12.5-16	25-32
Staphylococcus aureus (penicillin-sensitive), 101 isolates	90.1	94.1	99	100	—	—	—
Staph. aureus (not specified), 1,331 isolates	34.8	70.5	90.6	94.3	97.7	99.3	99.8
Staph. aureus (penicillinase-producing), 918 isolates	20.4	43.2	69.8	82.6	91.7	95.5	97.8
Staphylococcus (not specified), 278 isolates	38.1	70.1	87.8	91.7	97.8	—	100
Staph. albus, 195 isolates	12.3	75.9	93.8	94.9	—	95.4	96.4
Streptococcus pyogenes (beta-hemolytic), 307 isolates	95.1	98.7	—	—	—	—	99.3
Streptococcus (viridans group), 157 isolates	51.6	89.8	99.4	—	—	100	—
Diplococcus pneumoniae, 309 isolates	96.4	98.4	99.4	100	—	—	—

†Data compiled from published reports. Inoculum did not exceed 10^5 organisms per ml. in broth. Susceptibility patterns may vary from institution to institution.

Note: Many strains of enterococci, e.g., *Str. faecalis*, are relatively resistant. Some strains of staphylococci are resistant. *Pseudomonas* organisms are resistant, as are most indole-producing *Proteus* species and motile *Enterobacter* species.

excreted unchanged in the urine

rarely painful on I.M. administration

Guidelines for Loridine®
(cephaloridine, Lilly)

Before Administration

1. Determine renal status before *initiating* therapy.
2. In patients with renal impairment, reduced dosage should be employed. Other antibiotic therapy should be considered if impairment is due to acute tubular necrosis.
3. As with other antibiotics, appropriate specimens for culture and susceptibility testing should be obtained.
4. Use cautiously with other potentially nephrotoxic antibiotics (e.g., gentamicin, kanamycin, colistin, and polymyxin B), in penicillin-allergic patients, and in those receiving potent diuretics, such as furosemide or ethacrynic acid.

During Administration

1. Because of potential nephrotoxicity, daily dosages above 4 Gm. are not recommended for patients with normal renal function. The usual range for adults is 1.5 to 3 Gm. daily. In patients with renal impairment, recommendations in the package literature should be followed for *maintenance dosage* after a loading dose of 500 mg. to 1 Gm. If an endogenous creatinine clearance is considered more desirable than available BUN or serum creatinine concentrations for establishing the maintenance dosage, the initial loading dose may be given and results of that test obtained during the ensuing six or eight hours. If renal function improves during therapy, readjustment of dosage may be desirable.
2. Maintain proper hydration.
3. Monitor renal status. Renal impairment may be indicated by the appearance of urinary casts, proteinuria, oliguria, a rising BUN or serum creatinine, or a decreasing creatinine clearance or urine/plasma creatinine ratio.
4. If impaired renal function develops or worsens during therapy, discontinue use.

Lilly

300774

See next page for prescribing information.

---

*Due to susceptible organisms.

Loridine® (cephaloridine)

Because of nephrotoxicity (e.g., tubular necrosis) of cephaloridine in dosages above 4 Gm. daily (see Warnings and Adverse Reactions), recommended doses should not be exceeded. Renal status of the patient should be determined prior to initiation of therapy. Patients with known or suspected impairment of renal function should be under close clinical observation for changes in renal function or be hospitalized, and reduced dosage should be employed. If impaired renal function develops during therapy, cephaloridine should be discontinued.

Actions: *Human Pharmacology*—Peak blood levels of 7 and 14 mcg. per ml. respectively were obtained in one-half to one hour following intramuscular doses of 250 and 500 mg. in humans. Measurable levels of cephaloridine persisted for longer than twelve hours.

Loridine is excreted unchanged largely by glomerular filtration. Doses of 250 and 500 mg. produced very high antibacterial concentrations in the urine, in some instances approaching 1,000 mcg. per ml.

Its nucleus and degradation products differ from those of penicillin. However, some patients who are allergic to penicillin or to other cephalosporins may also be allergic to Loridine.

Microbiology—The in-vitro bactericidal action of Loridine results from inhibition of cell-wall synthesis. It is not bound significantly to plasma protein.

Loridine is active against the following organisms in vitro:

Beta-hemolytic and other streptococci (many strains of enterococci, e.g., *Streptococcus faecalis,* are relatively resistant)
Staphylococci, both coagulase-positive and coagulase-negative (some strains of staphylococci are resistant to cephaloridine)
Pneumococci
Gonococci
Hemophilus influenzae
Escherichia coli and other coliform bacteria
Klebsiella
Proteus mirabilis

Loridine is active against *Treponema pallidum* in animal studies.

All tested strains of group A streptococci, pneumococci, and penicillin-G-susceptible staphylococci are susceptible to Loridine. However, some strains of penicillinase-producing staphylococci are resistant in vitro to concentrations of Loridine that can be achieved in the serum. The majority of strains of *H. influenzae, Pr. mirabilis, Esch. coli,* and *Klebsiella* are also susceptible in vitro.

Pseudomonas organisms are resistant to Loridine, as are most indole-producing *Proteus* species and motile *Enterobacter* species.

Indications: Loridine is indicated in the treatment of serious infections of the respiratory tract, genito-urinary tract, bones and joints, bloodstream, soft tissue, and skin due to susceptible strains of the organisms listed above. It is also indicated for therapy of early syphilis when penicillin may be contraindicated. (*See* Warnings in regard to cross-sensitivity with penicillin.) It is indicated in the treatment of gonorrhea when penicillin is not considered the drug of choice.

Appropriate culture and susceptibility studies should be performed. If the susceptibility tests show that the causative organism is resistant to Loridine, other appropriate antibiotic therapy should be instituted.

Contraindications: Loridine is contraindicated in those persons who have shown hypersensitivity to it or other cephalosporins.

Warnings: **IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN C DERIVATIVES SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS. INSTANCES OF PATIENTS WHO HAVE HAD SEVERE REACTIONS TO BOTH DRUGS, INCLUDING DEATH FROM ANAPHYLAXIS, HAVE BEEN REPORTED.**

Impairment of renal function during treatment may be indicated by the appearance of casts in the urine, proteinuria, falling urinary output, a rising BUN or serum creatinine, or a decreasing creatinine clearance or urine/plasma creatinine ratio.

Cephaloridine should be given cautiously when used with other antibiotics having nephrotoxic potential, e.g., gentamicin, kanamycin, polymyxin B, and colistin.

The results of experimental studies in animals suggest that the concurrent use of potent diuretics, such as furosemide or ethacrynic acid, may increase the risk of renal toxicity.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions: In the case of infections due to beta-hemolytic streptococci, antibiotic therapy should be continued for at least ten days.

In the therapy of gonorrhea, patients in whom there is reason to suspect concomitant syphilis should have dark-field examinations of all suspect lesions before treatment and monthly serologic tests for a minimum of three months.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Superinfections may develop with organisms not in the spectrum of Loridine, particularly *Pseudomonas.* These can be recognized by clinical observation and by means of appropriate cultures. If they occur, proper therapeutic measures should be taken.

Since safety for use in premature infants and in infar
month of age has not been established, administration
dine to these patients is not recommended.

A false-positive reaction for glucose in the urine ma
Benedict's or Fehling's solution or with Clinitest® tablet
Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: *Hypersensitivity*—Maculopapular a
tous rashes, urticaria, and anaphylaxis have been re
fever and eosinophilia also have been noted. Hypers
actions are more likely to occur in patients with a hist
particularly to penicillin.

Blood—Neutropenia and leukopenia have been repor
dividuals have developed positive direct Coombs tests d

Liver—Transient elevations of transaminase and a
phatase levels have been noted. The significance of the
uncertain.

Renal—Severe, acute renal failure, in some cases t
death, has occurred in a small number of patients recei
The possibility of this complication seems to be greate
ill patients given more than recommended doses.
necrosis has been noted in affected patients coming to

Local Reactions—Pain on I.M. injection of Loridine
phlebitis on I.V. injection occurs infrequently.

Other—Nausea and vomiting have been reported.

Administration and Dosage: Ampoules should be protect
Extemporaneous mixtures of Loridine with other antibi
recommended.

Loridine should be dissolved in either Sodium Chlor
or Sterile Water for Injection (*see* the package literatur
table).

Intramuscular Injection—Loridine is usually injected
muscle mass, for example, the gluteal region or the
of the thigh.

The usual adult dosage for many infections of mod
is 500 mg. to 1 Gm. three times a day at equally spa
Milder and more susceptible infections have been trea
to 500 mg. given two or three times a day. More sev
may be treated with 500 mg. to 1 Gm. four times a day

A single 2-Gm. dose is recommended for the treatm
gonorrhea.

Early syphilis may be treated with 500 mg. to 1 Gm.
to fourteen days.

Although some clinical experience with high doses f
ening conditions has been reported, it has been shown t
dosages (above 4 Gm. daily) may cause serious neph
tions. For this reason, Keflin® (sodium cephalothin, L
preferred when doses larger than 4 Gm. daily are consi
threatening situations. If more than 2 Gm. of cephalori
ed daily, the patient should be under close clinical ob
changes in renal function or be hospitalized. In addit
dosage should be employed in patients with known
renal impairment (*see* the package literature).

In children, a daily total of 30 to 50 mg. per Kg. (15 t
pound) of body weight, given in divided doses, has been
tive for mild to moderately severe infections. A daily
mg. per Kg. (50 mg. per pound) of body weight (n
recommended adult doses) may be needed for very
tions. Since safety for use in premature infants and in i
one month of age has not been established, the use of
in these patients is not recommended.

In both adults and children, failures have appeared
more closely to insusceptibility of the organism or poor
dition of the patient than to inadequate dosage.

Intravenous Injection—In the presence of extremely
tions (such as bacteremia) or when any infection seem
ing, intravenous administration may be indicated.

Total daily dosages are the same as with intramuscu
For very susceptible organisms, 500 mg. to 1.5 Gm.
suffice; for less susceptible organisms and for serious
to 4 Gm. per day may be needed.

How Supplied: Ampoules Loridine® (cephaloridine, Lilly
250 mg., 5-ml. size, rubber-stoppered, in packages of
accompanied by six 20-ml. ampoules of Bacteriostatic
ride Injection, U.S.P.

500 mg., 5-ml. size, rubber-stoppered, in packages of
also available in packages of 50 (No. 772) accompanied
ampoules of Bacteriostatic Sodium Chloride Injection, U.

1 Gm., 10-ml. size, rubber-stoppered, in packages of
also available in packages of 25 (No. 773) accompa
20-ml. ampoules of Bacteriostatic Sodium Chloride Inj

[091372]

Additional information available to the profession
on request.

Eli Lilly and Company • Indianapolis, Indiana 46206

Worth using once

Made of 4-ply quilted cotton gauze with X-ray detectable element sewn into each sponge.

Pre-sterilized—always ready when you need them.

Double wrapped—for aseptic removal.

Disposable—to reduce the incidence of cross contamination.

Available in 4 sizes, with or without ring.

Write us for a sample and prices

SPARTA INSTRUMENT CORPORATION
305 FAIRFIELD AVENUE / FAIRFIELD, N.J. 07006 / (201) 575-1344

"Current abstracts are amplified and illuminated by comments of the members of the Editorial Board, based on their own clinical experiences as well as those of other recognized authorities" . . . just one of the reasons why Lippincott's

REVIEW OF
SURGERY

helps Resident (special rate only $11.00) and Veteran Surgeon alike to keep up with current progress, trends, and attitudes in all branches of surgery and the surgical specialties.

A true saver of precious reading time—from its detailed Contents Pages to its meaty reviews, and abstracts especially classified for reader convenience—a typical issue includes:

- Focus—several Reviews of timely or other special significance
- An original Report of major importance
- Twenty or more Abstracts with Commentary (and oft-times, rebuttal)
- Residents Corner—comprising Brief (1 to 3-page) Reports and Investigations
- In-depth Reviews of Current Books in Surgery

TO PUT THE BIMONTHLY REVIEW OF SURGERY AT YOUR FINGERTIPS NOW,

SUBSCRIBE TODAY . . .

J. B. LIPPINCOTT COMPANY, EAST WASHINGTON SQUARE, PHILADELPHIA, PA. 19105 A/S

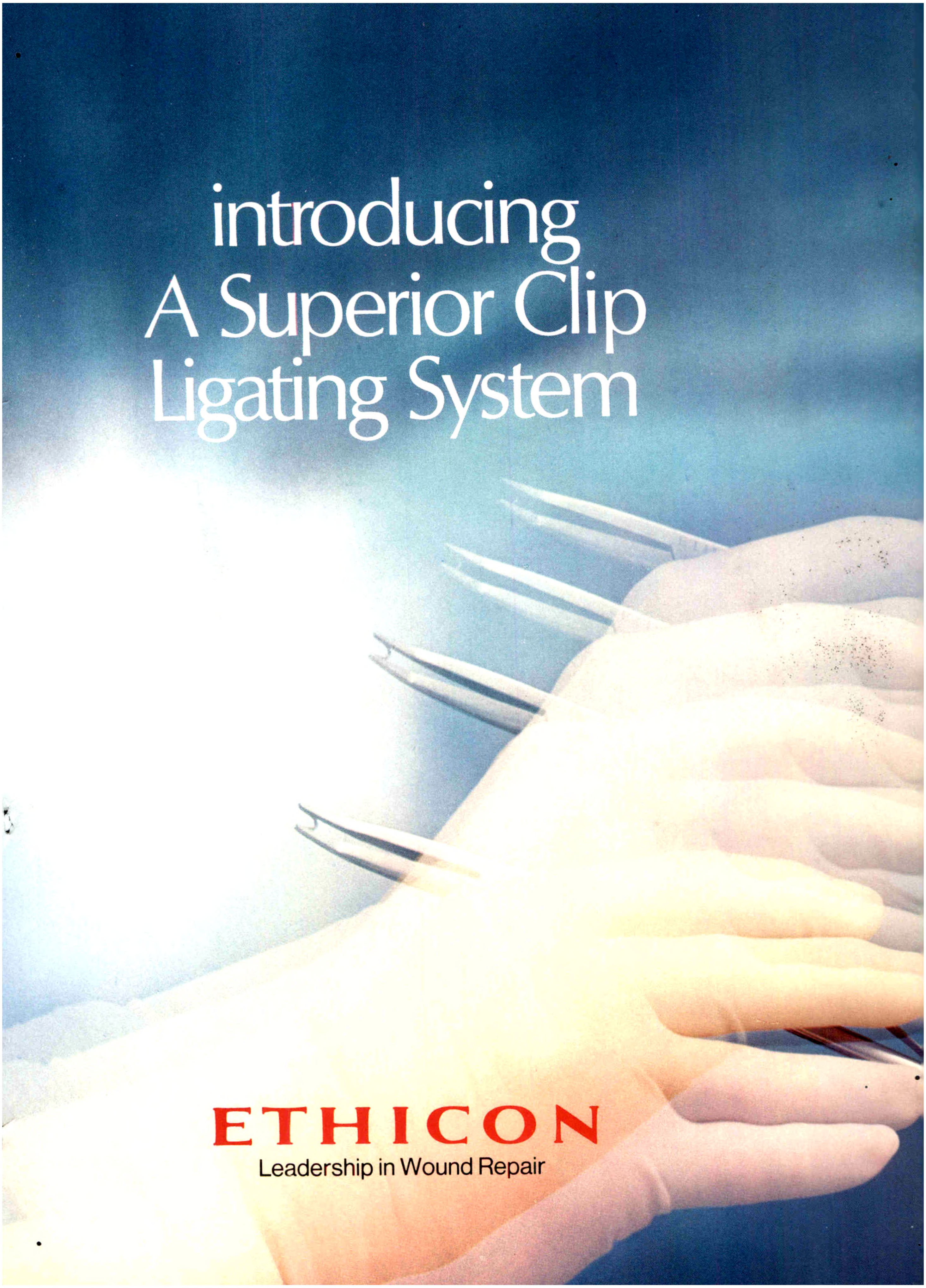
Please enter my subscription to REVIEW OF SURGERY for 1 year (6 issues), at ☐ $15 (U.S. and Canada); ☐ $17 (all other countries); Resident Rate ☐ $11 (U.S. only; also note "year" of residency and Specialty ____________).

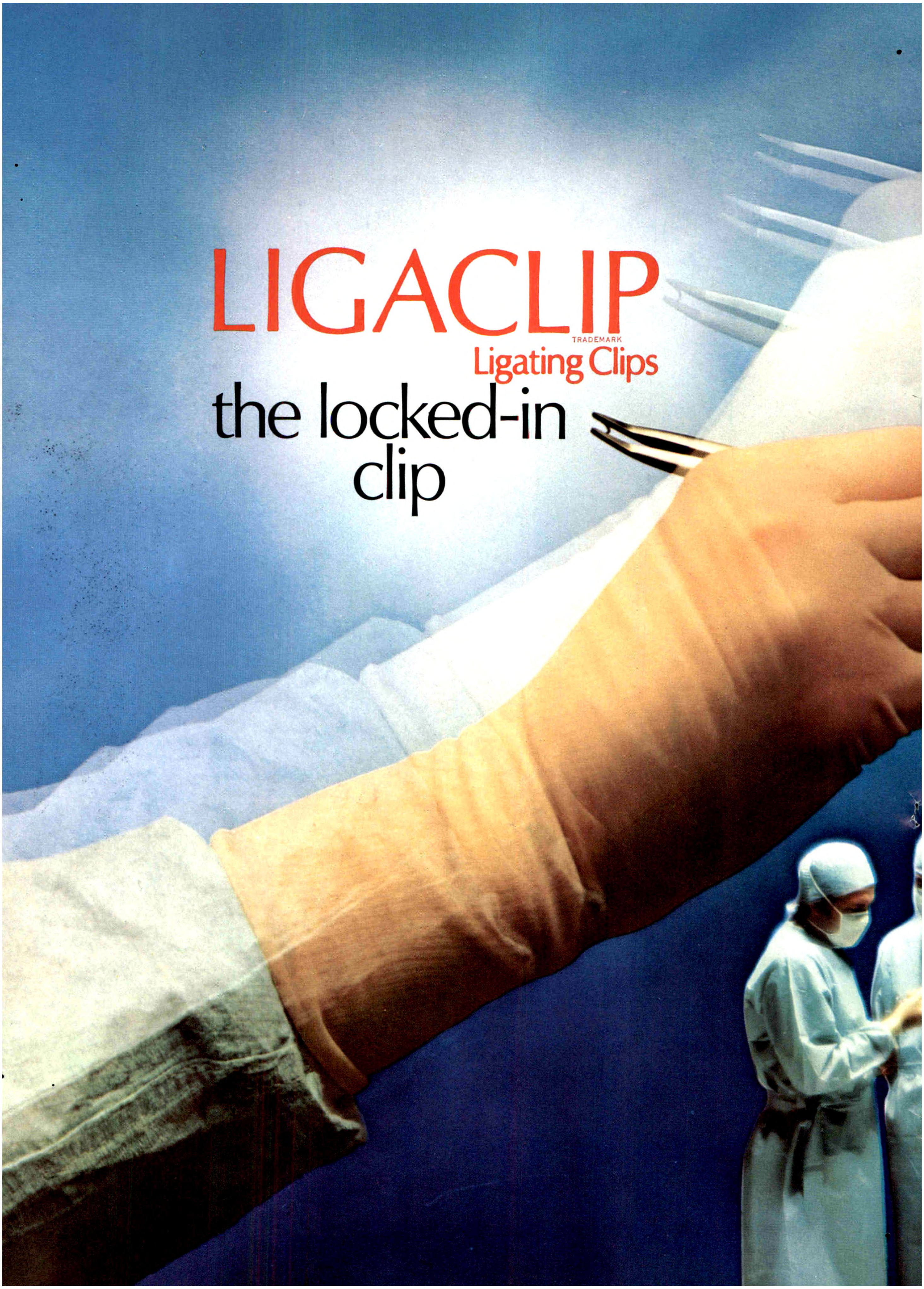
PLEASE PRINT ☐ Payment Enclosed.

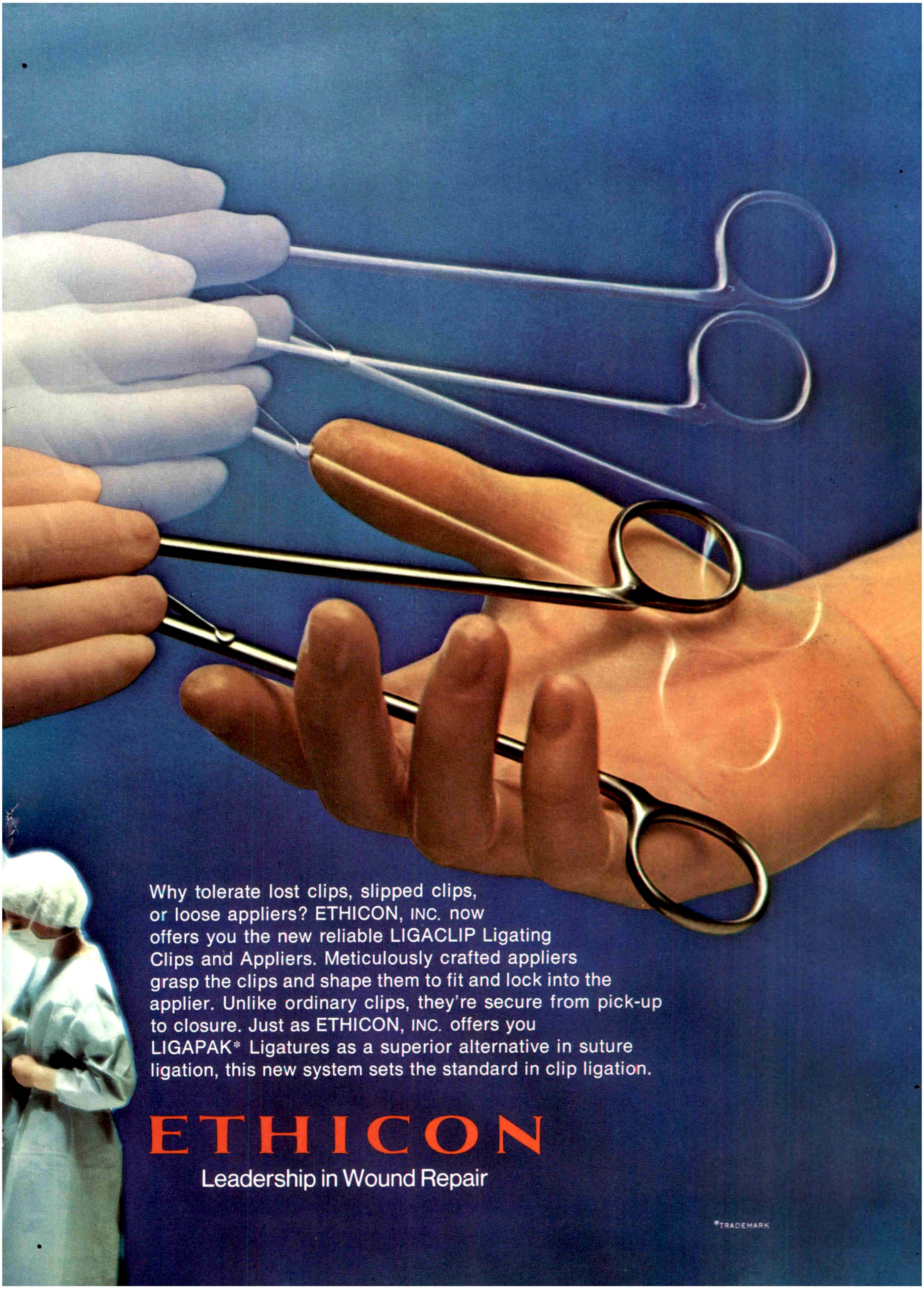
Name ____________ ☐ Charge my account.

Address ____________ My Specialty is:

City/State/Zip ____________ ____________


introducing
A Superior Clip
Ligating System
ETHICON
Leadership in Wound Repair


LIGACLIP
TRADEMARK
Ligating Clips
the locked-in clip



Why tolerate lost clips, slipped clips, or loose appliers? ETHICON, INC. now offers you the new reliable LIGACLIP Ligating Clips and Appliers. Meticulously crafted appliers grasp the clips and shape them to fit and lock into the applier. Unlike ordinary clips, they're secure from pick-up to closure. Just as ETHICON, INC. offers you LIGAPAK* Ligatures as a superior alternative in suture ligation, this new system sets the standard in clip ligation.

ETHICON
Leadership in Wound Repair

*TRADEMARK

LIGACLIP

TRADEMARK

Ligating Clips

unparalleled security from pick-up to closure

secure transfer

There's no need for you—or the nurse—to maintain tension during transfer since the clip is locked in the applier. Transfer is fast and secure.

accurate placement

The applier and clips are designed to provide accurate alignment. Twisting and slipping are virtually eliminated.

precise distal closure

When you apply pressure, the Tantalum clip forms a precise distal closure. Applier withdrawal is smooth and easy.

ETHICON Leadership in Wound Repair

© ETHICON, INC. 1973

340685

The Evaluation of A New Peritoneoscope As a Diagnostic Aid to the Surgeon

GEORGE BERCI, M.D., J. MANNY SHORE, M.D., JOEL PANISH, M.D.,
LEON MORGENSTERN, M.D.

*From the Departments of Surgery and Gastroenterology,
Cedars-Sinai Medical Center, Cedars of Lebanon
Hospital Division, Los Angeles, California*

THE VALUE OF PERITONEOSCOPY in the diagnosis of a host of pathologic conditions within the abdominal cavity is well established.[1,3,4,5,11,22] Nevertheless, some are still reluctant to use this procedure in the evaluation of difficult diagnostic problems. Reliance is generally based on clinical findings, biochemical assays, roentgenographic studies, radioactive scans, peritoneal lavage, or finally on diagnostic laparotomy. This may at times lead to undue delay in surgical correction of intra-abdominal problems, since the surgeon may be hesitant to undertake a laparotomy when he is uncertain about the indications.

Although this dilemma can be frequently resolved by peritoneoscopy, the procedure is seldom utilized. This can be attributed to lack of confidence in the technic, based on inexperience or dissatisfaction with instrumental performance. The recent development of a new image relaying system permitted the design of markedly improved instrumentation for peritoneoscopy in both adult and pediatric patients, and led us to re-evaluate this important examination. This report, based on 70 consecutive cases, describes advances in instrumentation and technic and delineates the usefulness of peritoneoscopy for the surgeon.

Instrumentation

Earlier investigators in this country, despite their wide experience,[14,24] did not gain many adherents. Inadequacy of existing instruments was probably responsible. Visualization through the older telescopes was poor compared with those available today. Moreover the larger diameter of the trocar (10–12 mm.) increased the danger of visceral injury during the abdominal wall penetration (Fig. 1).

The invention of the "rod-lens" system by Hopkins,[6] and related advances in instrument design (Fig. 2) made possible the production of scopes with trocars of only 7.0 mm. in diameter (Figs. 3 and 4).* This smaller size facilitates safe penetration of the abdominal wall. The increased light transmission, brighter image, improved resolution, wide viewing angle, and great depth of field of the miniaturized telescope, incorporating image and fiberlight transmission, facilitate prompt endoscopic orientation and manipulation. The excellent image quality contributes significantly to overall diagnostic precision.

A variety of manipulating and operating instruments have been developed. They can be safely introduced through a second smaller (5/5.5mm.) trocar under direct visual guidance. These can be used to expose areas which are covered by the omentum or other viscera. Some of these instruments are insulated so that a high-frequency current (cutting or coagulating) can be employed for hemostasis, lysis of adhesions, or definitive procedures such as tubal sterilization. Special biopsy forceps and a combined coagulation-suction device permit safe tissue sampling wherever indicated (Figs. 5 and 6). Additional accessories for photographic documentation and teaching are available.

Pneumo-peritoneum

This initial step requires meticulous attention to detail. A special pneumo-peritoneum needle containing a spring loaded blunt stillette (Fig. 7) prevents visceral

---

Submitted for publication April 28, 1972.

Reprint requests: George Berci, M.D. Division of Surgery, Cedars of Lebanon Hospital, 4833 Fountain Avenue, Los Angeles, California 90029.

* Manufactured by Karl Storz Medical Instrument Company, Tuttlingen, West Germany. Distributor: Storz Endoscopy America, Inc., 650 S. San Vicente Boulevard, Los Angeles, California 90048.

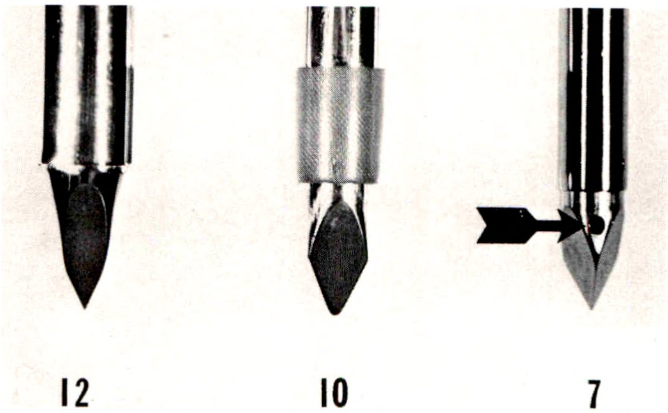


FIG. 1. Close-up of various trocars used for peritoneoscopy. From left to right: Diameters: 12 mm. 10 mm. (Ruddock) and 7 mm., described in text. Arrow indicates side hole in stilette which signals peritoneal entry.

perforation. During the insufflation of CO_2 or NO_2 the intra-abdominal pressure on the gauge of the insufflator (Fig. 8) is carefully monitored and maintained below 25 mm. Hg. A sudden rise to more than 30 mm. Hg signifies inflow obstruction, requiring prompt adjustment of the needle position. The volume of gas insufflated is unimportant, individual variations ranging between 3 and 12 liters. Additional guidance is provided by abdominal inspection and percussion for symmetrical distension, and by assessment of the tension of the abdominal wall. The flow should be intermittent to allow easier adaptation to the increased intra-abdominal pressure. The creation of an adequate protective gas-cushion by this technic will prevent intra-abdominal injuries due to the trocar puncture.

Clinical Experience

Peritoneoscopy was performed in 70 consecutive patients on the gastroenterologic, surgical and pediatric services of the Cedars-Sinai Medical Center between April 1970 and December 1971. Fifty per cent of the patients were over 60 years of age (Table 1). The examinations were carried out by 14 attending staff and three residents. The average hospital stay for patients undergoing peritoneoscopy only was 36 hours. Seven patients were safely returned by ambulance to the referring hospitals after a 4 to 6-hour period of observation in the recovery room following peritoneoscopy.

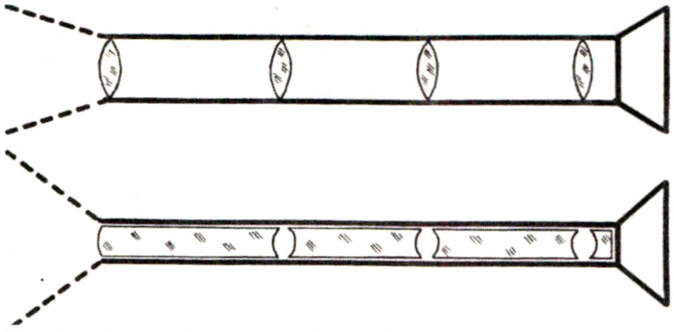


FIG. 2. Schematic diagram of telescopic systems used in endoscopy. *Top:* Conventional system—glass lenses are separated by air interspaces. *Bottom:* Hopkins "rod-lens" systems—air interspaces are replaced by glass rods with polished ends, separated by "air lenses." Advantages of this optical system are detailed in the text.

TABLE 1

Sex Distribution	
Male	34
Female	36
Age Distribution	
Years	*Number of Cases*
0–1	4
1–20	3
20–40	7
40–50	5
50–60	16
60–70	14*
70–80	16*
80–90	5*

* 35 cases (50%) were in the age group above 60.

The time required for the peritoneoscopic examination varied between 30 and 60 minutes. Additional time was required in some cases for aspiration of ascitic fluid, simultaneous cholangiography, multiple biopsies or other special procedures.

Anesthesia

Two-thirds of the patients were examined under general anesthesia, while one-third were satisfactorily evaluated under local anesthesia. With greater experience one is able to select more cases for local anesthesia, supplemented by adequate pre-medication. The cardiopulmonary status was monitored by an anesthesiologist in all cases.

Indications and Results

The various indications for peritoneoscopy in this series are shown in Table 2.

Evaluation of Liver Disease

Peritoneoscopy was indicated for the definitive evaluation of liver disease in 26 patients in whom precise diagnosis eluded the examiner despite clinical, laboratory, roentgenographic, radioisotope or histologic evaluation.

Cirrhosis

In five patients the diagnosis of cirrhosis was strongly suspected clinically, but could not be confirmed by liver function tests, radioisotope scans or percutaneous needle biopsy. In all cases the diagnosis was estab-

TABLE 2. *Indications*

Evaluation of Liver Disease			26
Cirrhosis	5		
Suspected hepatoma	7		
Suspected metastasis	11		
Hepatomegaly	3		
Abdominal Diagnostic Problems			38
Palpable mass		11	
Ascites		6	
Jaundice		6	
Gallbladder disease		3	
Staging of malignancy		2	
Mesent. vascular insufficiency		2	
Miscellaneous		8	
Pediatric			6
		Total	70

lished by peritoneoscopy with biopsy under direct vision using a special forceps (Fig. 5) introduced through a separate trocar.

Suspected Hepatoma

In seven patients with long standing cirrhosis the possibility of superimposed hepatoma was entertained clinically because of sudden deterioration of the patient's clinical course and/or liver function tests, the onset of a rapidly enlarging liver or right upper quadrant mass, or the appearance of a space occupying lesion on the liver scan. The existence of a hepatoma was definitively ruled out in all cases by peritoneoscopy. In one patient co-existence of liver metastases and cirrhosis was established.

Suspected Liver Metastases

In nine patients with known primary carcinoma, the presence of liver metastases was clinically suspected because of hepatomegaly, positive liver function tests and/or scans. Peritoneoscopic liver biopsy was performed rather than percutaneous needle biopsy because of the higher diagnostic accuracy and additional information provided by the former.[11,14,23] Three patients had histologically proven liver metastases, while the remaining six patients were shown to be free of dissemination. One patient was referred from another hospital with a diagnosis of metastatic carcinoma in the liver found by needle biopsy. Peritoneoscopy with liver biopsy revealed only cirrhosis with no evidence of malignancy in the liver or peritoneal cavity. The absence of malignancy was subsequently confirmed by exploration with multiple open liver biopsies. The patient remains clinically well during a 6-month follow-up period. In one additional patient without a known primary site, liver metastasis was suspected on the basis of the clinical picture and a positive scan, but was excluded by visualization of a normal liver.

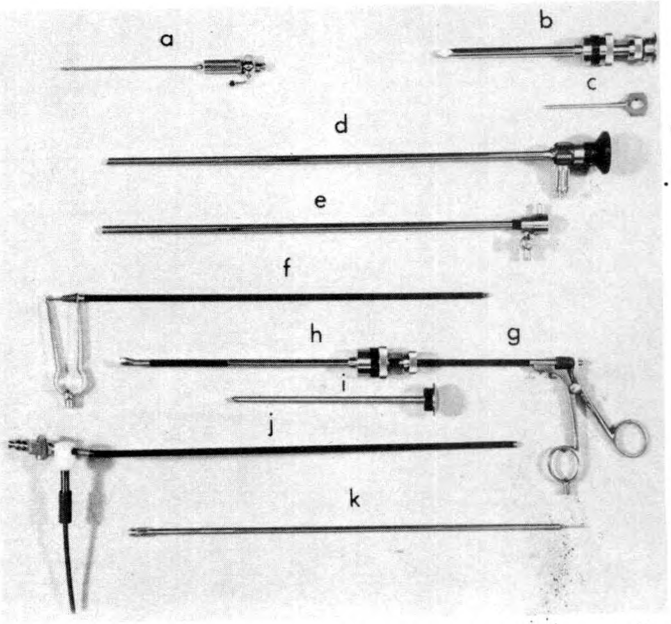


FIG. 3. Complete peritoneoscopy set. a: pneumo-peritoneum needle, b: examining trocar 7.0 mm. with c: desufflation key, d: 30° for-oblique telescope with fiber-light transmission, e: sheath for telescope with connection for gas-insufflation. Accessories: f: grasping forceps, insulated for electro-coagulation, g: biopsy forceps introduced through h: smaller trocar, 5.5 mm., i: stilette for above (h), j: insulated suction-coagulation probe, k: aspiration needle.

Hepatomegaly

Three patients presented with hepatomegaly of recent onset. Despite complete clinical, laboratory, radioisotope and roentgenographic evaluation, the cause could not be accurately established. In all cases a satisfactory explanation for the hepatomegaly was found: one patient had liver metastasis, one patient had anterior hepatic displacement due to a retroperitoneal process while the third patient, with a positive liver scan, was shown to have a normal appearing but caudally displaced liver.

Abdominal Diagnostic Problems

Peritoneoscopy was performed in 38 patients who had a variety of diagnostic problems. In each case the diagnosis remained obscure despite complete clinical, laboratory and X-ray evaluation so that in the absence of peritoneoscopic examination the next logical step in the diagnostic work-up would have been laparotomy.

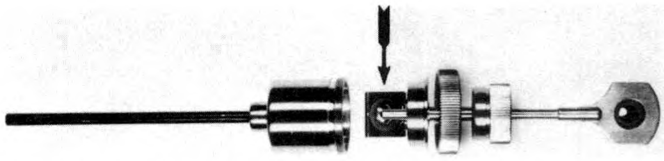


FIG. 4. Trocar disassembled to show opening of "no-escape" valve (arrow) by desufflation key.

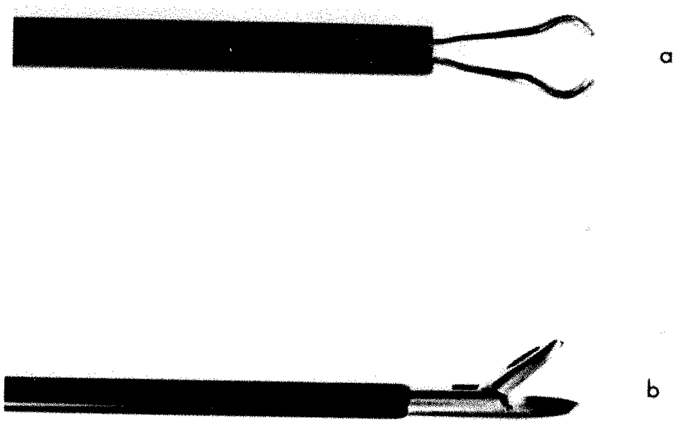


FIG. 5. Operating accessories: a: close-up of working end of insulated atraumatic grasping forceps. b: working end of tapered cutting edge biopsy forceps, particularly useful for deep liver biopsy.

Evaluation of Palpable Abdominal Mass

Eleven patients had palpable masses in the abdomen. In all cases an exploratory laparotomy was strongly considered for diagnosis and possible management. The presence of a lesion was excluded in three patients by visualization of normal anatomy at the site of the clinically suspected mass. In four patients peritoneoscopic examination disclosed widespread inoperable carcinoma either within the peritoneal cavity or the liver. All diagnoses were verified by biopsy. Three patients with known lymphoma were found to have involvement in the spleen or in the retroperitoneum, as shown by characteristic anterior displacement of the liver and stomach. In the final patient the mass was shown to be due to a benign neoplasm of the liver.

Ascites of Unknown Origin

Six patients had ascites for which the etiologic mechanism could not be established clinically. In all cases the cause was determined by peritoneoscopy. Three patients had advanced liver disease, (cirrhosis, chronic active hepatitis and hepato-portal sclerosis). Two patients with cytologically positive ascites had carcinomatosis of extra-ovarian origin, while in the remaining patient with chylous ascites a retroperitoneal mass was visualized.

The diagnosis was established by biopsy in all cases but the last.

Differential Diagnosis of Jaundice

In six jaundiced patients the etiology could not be determined after complete clinical evaluation, serial determination of liver function tests and a suitable period of observation. This well known dilemma is encountered in approximately 20% of icteric patients.

Peritoneoscopy led to the correct diagnosis in all cases. Cholangiography under peritoneoscopic guidance was added in three cases. Three patients were found to have extrahepatic biliary obstruction, indicating prompt exploration (Table 7). In the remaining three cases extrahepatic obstructive jaundice was ruled out and laparotomy was avoided.

Diagnosis of Gallbladder Disease

Under certain circumstances conventional roentgenographic methods do not confirm the presence of gallbladder disease which is clinically suspected:

a. The contrast material may not be excreted in adequate concentration because of impaired liver function.
b. A recent bout of acute pancreatitis may temporarily impair gallbladder function.
c. In patients with iodine sensitivity the study is contraindicated.

Three patients undergoing peritoneoscopy in this study fell within the above categories. In one patient the reason for nonvisualization was attributable to cirrhosis and laparotomy was avoided. In the other two patients the peritoneoscopic finding of pericholecystic adhesions or inflammatory change established the diagnosis of gallbladder disease, indicating the need for surgical intervention.

Staging of Intra-abdominal Carcinoma

In two patients with radiologically demonstrated large malignancies the feasibility of radical resection was evaluated by peritoneoscopy. In one patient with

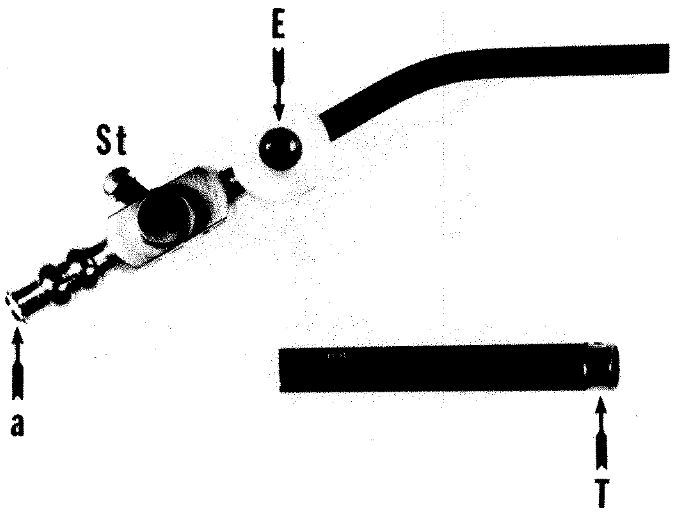


FIG. 6. Close-up of working part of insulated suction-coagulation probe. a: connection for suction, ST: stopcock for digital control of interrupted suction, E: connection to electro-coagulation, T: combined suction-coagulation tip.

carcinoma of the stomach, the visualization of unsuspected peritoneal metastases precluded the advisability of laparotomy. In the second patient with extensive carcinoma of the sigmoid colon, resectability could not be assessed from the peritoneoscopic findings.

Mesenteric Vascular Insufficiency

The difficulty of establishing the diagnosis of mesenteric vascular insufficiency or intestinal infarction is well recognized. Peritoneoscopy was performed in two patients in whom this diagnosis was strongly suspected clinically. By visualizing the surface of the intestine it was possible to exclude mesenteric vascular insufficiency in one patient, while in the second case an area of localized gangrene was identified, leading to prompt laparotomy.

Pediatric

Six patients ranging in age from 1 day to 7 years underwent peritoneoscopy. Experience with pediatric endoscopy at this institution is separately described in another publication.[10]

Complications

Complications encountered during peritoneoscopy were minimal.[20] Three patients exhibited cardiac arythmias during CO_2 insufflation which were reversed by immediate partial desufflation. Slow, intermittent reinsufflation was subsequently well tolerated. Emphysema of the mesentery due to faulty needle placement was seen in two patients. This was recognized during insufflation and was corrected by changing the position of the needle. Transient postoperative paralytic ileus resulted in one patient. Subcutaneous emphysema of the abdominal wall occurred in one patient; further extenson was avoided by reintroduction of the pneumoperitoneum needle. Two patients with carcinomatosis peritonei subsequently developed tumor implants at the puncture site.

Visceral injury, intra-abdominal hemorrhage, peritonitis or wound infection were not encountered in this series. There was no mortality attributable to the procedure. One patient died 3 weeks postoperatively of metastatic melanoma.

Discussion

Peritoneoscopy was performed in 70 consecutive patients. Diagnosis was established in 62 cases (90%). In the remaining eight patients (10%) the examination was of no assistance (Table 3). In 44 patients diagnosis was achieved by biopsy while in 18 patients the diagnostic conclusion was based on endoscopic findings. The latter were confirmed by surgical exploration in seven cases; in the remaining 11 patients, visualization of either normal viscera or grossly recognizable lesions precluded the need for biopsy (Table 4).

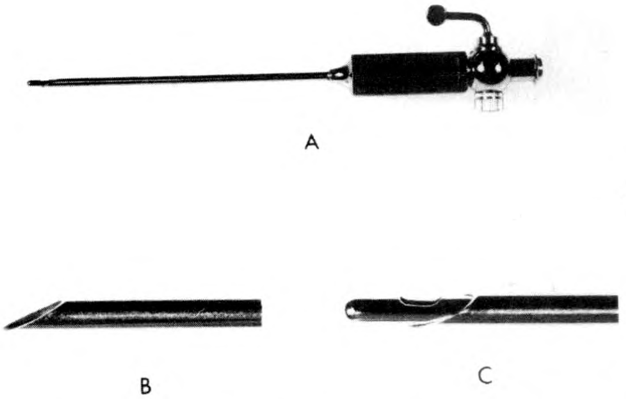


FIG. 7. Pneumo-peritoneum safety needle. A: needle with spring loaded blunt stilette, and stopcock. B: close-up of needle tip, blunt stilette is automatically pushed by resistance of abdominal wall during insertion. C: blunt stilette with side hole for insufflation springs forward as soon as needle enters peritoneal cavity.

Of the entire group, 38 patients were strongly considered for diagnostic laparotomy after thorough clinical, laboratory and X-ray examination. Peritoneoscopy led to a diagnosis in 27 patients (71%), thus eliminating the need for laparotomy (Tables 5 and 6). The presence of inoperable malignancy was established in 14 patients; mechanical obstruction was excluded in four jaundiced patients; clinically suspected masses

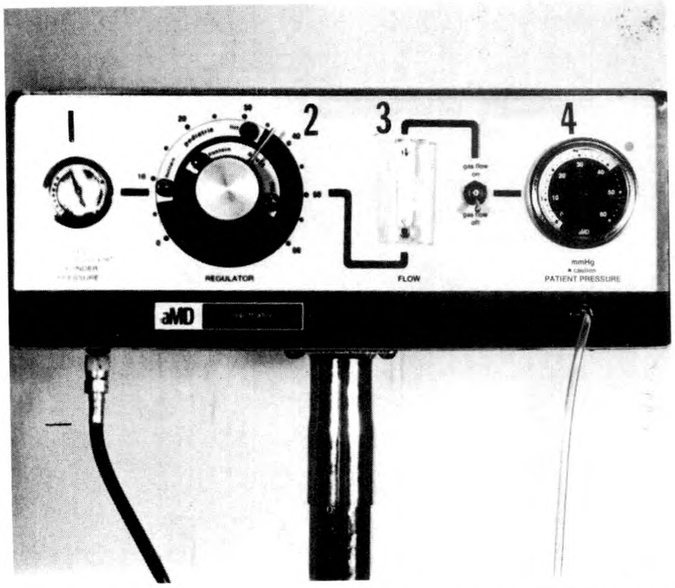


FIG. 8. Pneumo-peritoneum insufflator* (CO_2 or NO_2). 1) Gas cylinder pressure indicator dial. 2) Fully automatic pressure control. Range: 0-50 mm. Hg. 3) Flow-indicator. 4) Intra-abdominal pressure gauge. Danger zone (over 40 mm. Hg) is clearly displayed.

---

* Manufactured by Automated Medical Devices Corporation, Suite 635, 1800 Avenue of the Stars, Los Angeles, California 90067

TABLE 3. *Diagnostic Accuracy*

Diagnosis unknown		70 (100%)
Diagnosis established		62 (90%)
Microscopic	44	
Macroscopic	18*	
Not diagnostic		6 (8%)
Unsuccessful		1 (2%)

* Confirmed by exploration: 7

were ruled out by visualizing normal structures in four instances, and a variety of diagnostic problems was resolved by the peritoneoscopic findings in a miscellaneous group of five patients (Table 6).

In nine patients the peritoneoscopic findings confirmed the necessity for exploration (Table 7). Biliary tract obstruction was identified in four jaundiced patients. In two patients with suspected cholecystitis in whom radiologic diagnosis failed, peritoneoscopy identified a surgically correctable biliary tract lesion. In one case an area of localized intestinal infarction was visualized, while in the remaining patient with sarcoidosis, a pelvic mass was identified as chronic pelvic inflammatory disease.

Appropriate management in the above group of 38 patients was thwarted by inability to pinpoint the diagnosis. An indication for diagnostic laparotomy was present in all cases. Continued observation may have committed some patients to increase morbidity due to delay in management (Table 7). Peritoneoscopy resolved the diagnostic problem in 95% of these cases; laparotomy was rendered unnecessary in 27 (71%), and was shown to be clearly indicated in nine patients (24%) (Table 5).

TABLE 4. *Diagnosis Established by Visualization*

Case No.	Clinical Diagnosis	Peritoneoscopic Diagnosis
3	Liver metastases	Normal liver
55	Liver metastases	Normal liver
70	Liver metastases	Normal liver
5	Abdominal tumor?	Normal abdomen
56	Pelvic tumor	Uterine fibroids
43	Abdominal tumor	Splenomegaly
11	Cholecystitis	EHO (Metastatic carcinoma)*
61	Jaundice	EHO (Chronic pancreatitis)*
63	Jaundice	EHO (Carcinoma of pancreas)*
65	Metastatic Ca.	EHO (Metastatic carcinoma)*
9	Non-visualized gallbladder	Cirrhosis, normal gallbladder
16	Hepatoma?	Cirrhosis
68	Hepatoma?	Cirrhosis
6	Pancreatitis	Cholecystitis*
8	Mesenteric vascular insufficiency	Normal intestine
67	Mesenteric vascular insufficiency	Intestinal infarction*
10	Pediatric inguinal hernia	Unilateral hernia
21	Pelvic mass	Chronic pelvic inflammatory disease*

* Confirmed by exploration (7)
EHO: Extrahepatic biliary obstruction

TABLE 5. *Peritoneoscopy Versus Laparotomy*

	No. Cases	%
Exploration clinically indicated	38	100
Exploration avoided	27	71
Exploration performed—(indication confirmed)	9	24
Peritoneoscopy inconclusive	2	5

TABLE 6. *Laparotomy Avoided by Peritoneoscopy*

		No. Cases
Inoperable malignancy		14
Icterus (non surgical)		4
Palpable mass		4
Miscellaneous		5
Fever, unknown origin	1	
Mesent. vasc. insuff. (?)	1	
Non-visualized gallbladder	1	
Ovarian tumor (?)	1	
Hepatomegaly (pediatric)	1	
Total		27

The value of peritoneoscopy is further appreciated when its diagnostic accuracy is compared with other modalities available.

The comparative accuracy of peritoneoscopy and liver scan could be ascertained in 27 patients (Table 8). The radioisotope diagnosis was found to coincide with the peritoneoscopic findings in only 12 patients (44%). False-positive (27%) or false-negative (10%) findings were reported by scan in an additional 10 patients, while in the remaining five patients (19%) with inconclusive scans, a specific lesion was identified by peritoneoscopy.

The limitations of percutaneous needle biopsy of the liver are well documented.[16,17,19] In patients with cirrhosis, Schoenfield *et al.* have recently reported 30% false-negative results with needle biopsy.[18] In patients with suspected liver metastases, false-negative needle biopsies are not uncommon.[8,19] The presence of hepatoma in cirrhotics is difficult to confirm by needle biopsy.

Biopsy under peritoneoscopic control eliminates these disadvantages. Not only can much of the liver be visualized but the distribution of the lesions can be ascertained. This permits biopsies to be obtained from the optimal location. Bleeding from the biopsy site is readily recognized and can be arrested. In this series there were 26 patients with suspected liver disease. Diagnostic biopsy under visual control was obtained in 24. In the remaining two, a biopsy was not attempted since a normal liver was visualized.

In approximately 20% of jaundiced patients special diagnostic procedures are required to identify the pres-

TABLE 7. *Indication for Laparotomy Confirmed by Peritoneoscopy*

		Diagnosis	
Case No.	Clinical	Peritoneoscopic	Operative
11	Chron. Cholecystitis (?)	Chron. Cholecystitis	CBD obstruction due to metast. Ca.
64	Metast. Ca. Liver	*Hemochromatosis*	*Hemochromatosis*
6	Pancreatitis	*Cholecystitis*	*Cholecystitis* and pancreatitis
57	Icterus unknown etiol.	*Biliary Atresia*	*Biliary Atresia*
61	Icterus unknown etiol.	*CBD obstruction* extrinsic	*CBD obstruction* due to Ca. of pancreas.
63	Icterus unknown etiol.	*Extrahep. biliary obstruction.*	*Extrahep. biliary obstruction* due to Ca. pancreas.
65	Metast. Ca. liver vs. periductal node metast.	*Extrahep. biliary obstruction.*	*Extrahep. biliary obstruction* due to metast. Ca.
67	Mesent. vascular insufficiency	*Intestinal infarction*	*Intestinal infarction*
21	Pelvic mass, Sarcoidosis	*Chron. Pelvic inflamm. disease*	*Chron. Pelvic inflamm. disease*

ence of mechanical obstruction. To date, the most promising diagnostic aid has been percutaneous transhepatic cholangiography.[2,9,12] However, analysis of reported series reveals that in the majority of patients in whom ductal visualization by this procedure is not obtained, the patient still harbors a surgical lesion (Table 9).

For this reason it is anticipated that greater diagnostic accuracy may be achieved by peritoneoscopy whenever percutaneous transhepatic cholangiography fails to visualize the biliary tract. In some patients it is possible to clearly establish the diagnosis by the peritoneoscopic findings alone;[7,15] where this is not possible, one has the advantage of being able to place the needle more accurately within the liver substance. Should transhepatic duct puncture not result, one still has the option of puncturing the visualized gallbladder through a transhepatic approach.[13,21] The danger of bile leak following direct gallbladder puncture[13] is thus eliminated by liver tamponade. This is particularly important when a surgical lesion is excluded and laparotomy does not follow cholangiography. This method can also be useful in demonstrating biliary calculi where standard cholecystography is inconclusive or contraindicated.[21]

The difficulty of establishing a clinical diagnosis of acute mesenteric vascular insufficiency even when it is strongly suspected is well known. Diagnostic accurracy here is crucial because of the increased risk of laparotomy. Variants of this syndrome, which may be amenable to non-operative management, could also be hopefully identified. Experience with this new entity is currently too limited to warrant proper evaluation and remains within the experimental domain of peritoneoscopy.

In many patients with carcinoma of the breast and lung, liver metastases may appear within the early post-resection period. Peritoneoscopy in patients with positive biopsies may have a place as a method of staging prior to definitive therapy. Of five patients evaluated in this category, one was found to have liver metastasis by peritoneoscopy 3 months following radical mastectomy.

The miniaturized instruments offer the possibility of peritoneoscopic evaluation in newborns and infants. Previously these diagnostic areas could be approached only by laparotomy since needle biopsy is extremely difficult to perform in these patients. Experience with pediatric peritoneoscopy at this institution is described in greater detail in a separate communication.[10]

While peritoneoscopy has been in use for over 60 years, its widest application has been relegated to the gynecologist and the gastroenterologist. Acceptance of this important diagnostic procedure by the general surgeon has been exceedingly slow. Before recom-

TABLE 8. *Comparison of Liver Scan and Peritoneoscopy (27 Cases)*

No. Cases	Scan	Peritoneoscopy
7	Positive (C = 3, T = 4)	Positive (C = 3, T = 4)
5	Negative	Negative
7	Positive	Negative
3	Negative	Positive (C = 2, T = 1)
5	Inconclusive	Positive (C = 4, T = 1)

C = Cirrhosis
T = Tumor

TABLE 9. *Differential Diagnosis of Jaundice Accuracy of Percutaneous Cholangiography*

Author	Date	No. Jaundiced* Pts.	% Surgical Lesions in Non-Visualized Cases
Seldinger	1962	70	70%
Evans	1966	140	60%
Ritchie	1969	54	50%
Sherlock	1965	137	43%
Blake++	1965	559	24%
Flemma	1966	107	20%
Kaplan	1964	40	20%
Wiechel	1964	60	0%

* 80–90% of entire series are surgical
++ Collected series

mending an exploratory laparotomy, strong consideration should be given to peritoneoscopy, which can often provide the same information. Moreover, reduction in mortality and morbidity, as well as socio-economic factors, must be borne in mind when comparing the diagnostic choices available.

Summary

1. Advances in optics and instrumentation have led to the introduction of a new peritoneoscope. Several manipulating, tissue sampling and hemostatic accessories have resulted in a significantly improved and safer examination technic.
2. The usefulness of this technic is analyzed in 70 consecutive cases:
   a. The overall diagnostic accuracy was 90%.
   b. In 38 patients with indications for diagnostic laparotomy the correct information was provided in 95%; laparotomy was avoided in 27 patients (71%).
   c. The morbidity was negligible.
   d. No mortality was encountered.
3. The applications of peritoneoscopy into special diagnostic areas, such as the differential diagnosis of jaundice, mesenteric vascular insufficiency and pediatrics are recommended.

Addendum

Since this manuscript was submitted 50 additional patients with abdominal diagnostic problems have undergone peritoneoscopy. Indications, results and complications of this added experience are identical to that presented in this paper.

Acknowledgment

We are indebted to the staff members of the Departments of Surgery, Gastroenterology and Obstetrics and Gynecology, for their collaboration.

References

1. Anderson, J. R., Dockerty, M. B. and Waugh, J. M.: Peritoneoscopy: An Evaluation of 396 Examinations. Proc. Mayo Clin., **25**:601, 1950.
2. Arner, O., Hagberg, S. and Seldinger, S. I.: Percutaneous Transhepatic Cholangiography. Surgery, **52**:601, 1950.
3. Beck, K.: Color Atlas of Laparoscopy. Schattauer Publisher, New York, Stuttgart, 1970.
4. Berci, G.: Advances in Endoscopy. Med. J. Aust., **2**:653, 1962.
5. Berci, G.: Peritoneoscopy. Br. Med. J., **1**:562, 1962.
6. Berci, G., Kont, L. A.: A New Optical System in Endoscopy. Br. J. Urol., **41**:654, 1969.
7. Boyce, H. W.: Differential Diagnosis of Jaundice. Postgrad. Workshop on Peritoneoscopy, Cedars of Lebanon Hospital, Los Angeles, March 1972.
8. Conn, H. O.: Rational Use of Liver Biopsy in the Diagnosis of Hepatic Cancer. Gastroenterology, **62**:142, 1972.
9. Evans, J. A., Glen, F., Thorbjarnarson, B. and Mujahed, Z. Percutaneous Transhepatic Cholangiography. Radiology, **78**:362, 1962.
10. Gans, S. and Berci, G.: Advances in Endoscopy of Infants and Children. J. Ped. Surg., **6**:Suppl. April 1971.
11. Kalk, H.: Leitfaden Der laparoskopie und Gastroskopie, Thieme, Stuttgart, 1951.
12. Ritchie, G. W., Jackson, D. C. and Eaglesham, H.: Percutaneous Transhepatic Cholangiography: Experience with 54 Cases. Can. Med. Assoc. J., **100**:110, 1969.
13. Rosenbaum, F. J.: Die Laparoskopische Cholangiographie. Klin. Wschr., **33**:39, 1955.
14. Ruddock, J. C.: Peritoneoscopy: A Critical Clinical Review. Surgical Clinics of North America, October 1957, p. 1249.
15. Ruddock, J. C.: Peritoneoscopy. Surg. Gynecol. Obstet., **65**:623, 1937.
16. Schiff, L.: The Clinical Value of Needle Biopsy of the Liver. Ann. Int. Med., **34**:948, 1951.
17. Schiff, L.: Disease of the Liver. In Needle Biopsy of the Liver, Lippincott, Philadelphia. 1969.
18. Soloway, R. D., Baggenstoss, A. H., Schoenfield, L. J. and Summerskill, D. M.: Observer Error and Sampling Variability Tested in Evaluation of Hepatitis and Cirrhosis by Liver Biopsy. Digest. Dis. **16:12**:1082, 1971.
19. Sherlock, S.: Aspiration Liver Biopsy; Technique and Diagnostic Application. Lancet, **2**:397, 1945.
20. Vilardell, F., Seres, I. and Marti-Vicente, A.: Complications of Peritoneoscopy. A Survey of 1,455 Examinations. Gastrointest. Endosc., **14**:178, 1968.
21. Wannagat, L.: Die laparoskopische Cholecysto-und Cholangiographie im Roentgenbild und Farbphoto. Verb. Deutsch. Ges.f.inn. Med. (60th Congress Report) Bergmann, Munich, 1954.
22. Wittman, I.: Peritoneoscopy Vol I—II, Academic Press Budapest, 1964.
23. Zamcheck, N. and Sidman, R. L.: Needle Biopsy of the Liver. I. Its use in Clinical and Investigative Medicine. N. Engl. J. Med., **249**:1020, 1953.
24. Zoeckler, S. J.: Peritoneoscopy: A Revaluation. Gastroenterol., **34**:969, 1958.

Non-Surgical Management of Cystic Hydatid Disease in Alaska:

A Review of 30 Cases of Echinococcus Granulosus Infection Treated without Operation

L. W. PINCH, M.D., J. F. WILSON, M.D.*

From the Surgical Service, Alaska Native Medical Center, U.S. Public Health Service, Anchorage, Alaska

HYDATID DISEASE caused by the sylvatic (forest-wild animal cycle) form of *Echinococcus granulosus* (Batsch, 1786) which is indigenous to Alaska and Canada differs in important ways from that caused by the more widely occurring pastoral form of *E. granulosus* of European origin. The more benign nature of the disease caused by the sylvatic form was pointed out earlier in a report based on 101 cases from Alaska[11] and by Meltzer's report[5] of 180 cases from Canada. The absence of the classical complications, such as dissemination and anaphylaxis, in infections caused by the sylvatic form suggested that this type of hydatid disease did not necessarily require the aggressive surgical treatment recommended for the pastoral type. Consequently, in 1966, we elected to change our management of these cysts from a surgical to a largely non-surgical approach. It is the purpose of this communication to report the progress and results of this conservative method of treatment.

Observations

Since 1966 we have evaluated 32 patients (25 previously unreported) with the diagnosis of a pulmonary *Echinococcus granulosus* cyst. Of these, 30 patients were treated without pulmonary resection and they provide the basis of this report. In the other two patients the lesions were resected to rule out malignancy.

All of these patients came from areas of Alaska where *E. granulosus* is known to occur.[3] Most of the patients lived in central, interior Alaska. All patients had had contact with dogs around the home and eight persons specifically asked, acknowledged that their dogs had been fed the lungs of moose or caribou. In Alaska, dogs infected in this way are almost invariably the source of infection for man. The median age of the 30 patients was 26, with a range of 8 to 106 years. There were 18 males and 12 females. All had cysts in the lungs, and three had calcified cysts in the liver also. Two patients had two pulmonary cysts each. Intradermal skin tests[4] for *E. granulosus* were administered to 10 patients. Five of the tests were positive.* Indirect hemagglutination tests[4] of 16 patients produced only three positive results. Two of the positive cases were in patients with previously ruptured cysts.

Two children were initially admitted with ruptured infected cysts complaining of fever and cough. Chest films showed evidence of pneumonia. One child required tube drainage of the infected cyst and the other responded to antibiotics. The remaining 28 patients with 30 unruptured cysts were asymptomatic at the time their disease was discovered by routine chest radiography. Pertinent points from the clinical case histories follows:

In three older patients, needle aspiration of the cyst was carried out under fluoroscopic control to rule out

---

Submitted for publication April 13, 1972.

Reprint requests: J. F. Wilson, M.D., Alaska Native Medical Center, P.O. Box 7-741, Anchorage, Alaska 99510.

* The refined skin test for *Echinococcus* from the Center for Disease Control, Atlanta, Ga. was used. A positive reaction was considered to be a wheal 1.2 cm. or greater.

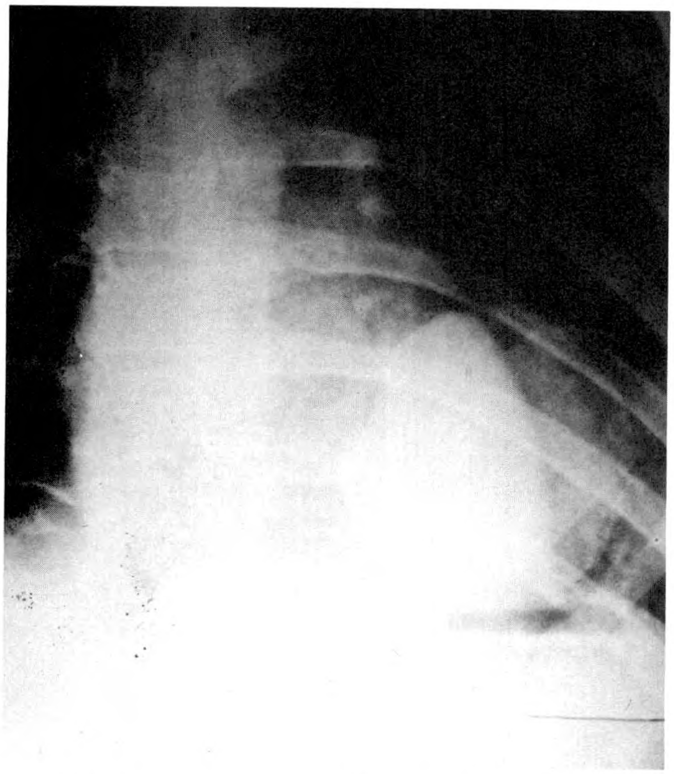


FIG. 1. PA chest roentgenograms of a 15-year-old girl: A. a large asymptomatic pulmonary Echinococcus cyst which had been followed for 1 year. The diameter of the cyst was 6.8 × 7 cm.

malignancy. The diagnosis of echinococcosis was confirmed by the identification of protoscolices in the aspirate. One of these patients had complications from the procedure—a small pneumothorax with pleural effusion and some local pneumonitis. These complications were of minor clinical significance and cleared rapidly. Twenty-five patients with 27 cysts were followed by periodic chest radiography. Twelve cysts remain intact and asymptomatic at the time of this writing. Fifteen cysts have ruptured spontaneously during the period of observation. In two patients, rupture of the cyst produced mild symptoms; wheezing in one, cough and fever in the other. Three patients gave a history of expectorating fluid and four had asymptomatic infiltrations in the area of the cyst on radiography. In the remaining cases the cysts silently disappeared on follow-up chest films. The median period of observation at the time of rupture was 2 years; and on the last examination prior to rupture the average diameter of the cyst was 3.5 cm.

No patient had symptoms which persisted beyond the first few weeks after initial rupture. No patients have died, and none has had any serious morbidity.

Discussion

A non-surgical approach to the treatment of the relatively benign sylvatic form of *E. granulosus* cysts indigenous to Alaska and Canada was initiated in 1966 and appears to have produced good results. No serious problems occurred in a series of 30 patients who were followed for an average of 2.5 years. Thirteen of 15 patients with spontaneous rupture of cysts were unaware that the cysts had ruptured, with the exception that three patients expectorated fluid. The serial chest roentgenograms of the two patients shown in Figures 1 and 2 were typical of those in whom the cysts silently disappeared.

The diagnosis of pulmonary cystic hydatid disease in Alaska usually is based on the following characteristics: The patient comes from an endemic area of the state and has a positive history of association with dogs. He is usually young. (The median age in this series was 26 and in 66 patients previously reported, it was 22 years.) He comes in for evaluation of a discrete pulmonary lesion incidentally found on routine chest films. The roentgenologic appearance of the lesion is usually typical although the classical pathognomonic signs (*i.e.* the "water lily" and "crescent" signs) have been observed only rarely. Lesions are characteristically round or oval (depending to some extent on lung expiration or inspiration) with a very homogenous appearance and

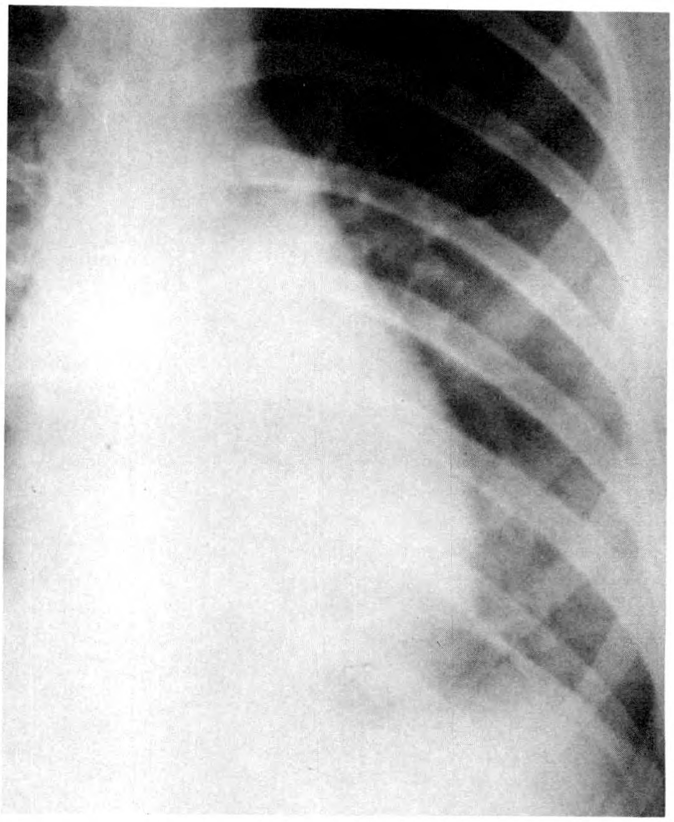


FIG. 1B. Routine follow-up chest film taken 6 months later showing that the cyst had silently disappeared. The patient was unaware that the cyst had ruptured and has remained asymptomatic following rupture for 4 years.

with a water-like density. These lesions usually have clear-cut borders with very little or no reactive changes around them. Occasionally the cysts may be somewhat lobulated. They can be located anywhere in the lung. These characteristics usually allow for an accurate diagnosis. Prior to 1966 when resection was the treatment of choice, only one of 54 patients with a preoperative diagnosis of echinococcus cyst was found not to have a cyst. This patient had a benign lesion. Patients in the cancer-age group who are believed to have hydatid cysts require further diagnostic studies including sputum cytology and planography of the pulmonary lesion. If the lesion is peripheral, needle aspiration is thought to be safe in the sylvatic form of the disease since anaphylaxis or seeding of the cysts has never been reported. Because of the risk of such complications, needle aspiration of cysts of the pastoral form is contraindicated.[10] Three of our patients underwent needle aspiration without serious sequelae. If there is basis for considerable suspicion of cancer, an open thoracotomy is recommended.

Serologic tests and intradermal skin tests were not done in all of our patients. The results have not shown the tests to be very reliable in the diagnosis of *E. granulosus.* This is confirmed by others.[6,7] If the cyst has been leaking fluid or has ruptured, these tests are usually, though not invariably, positive.

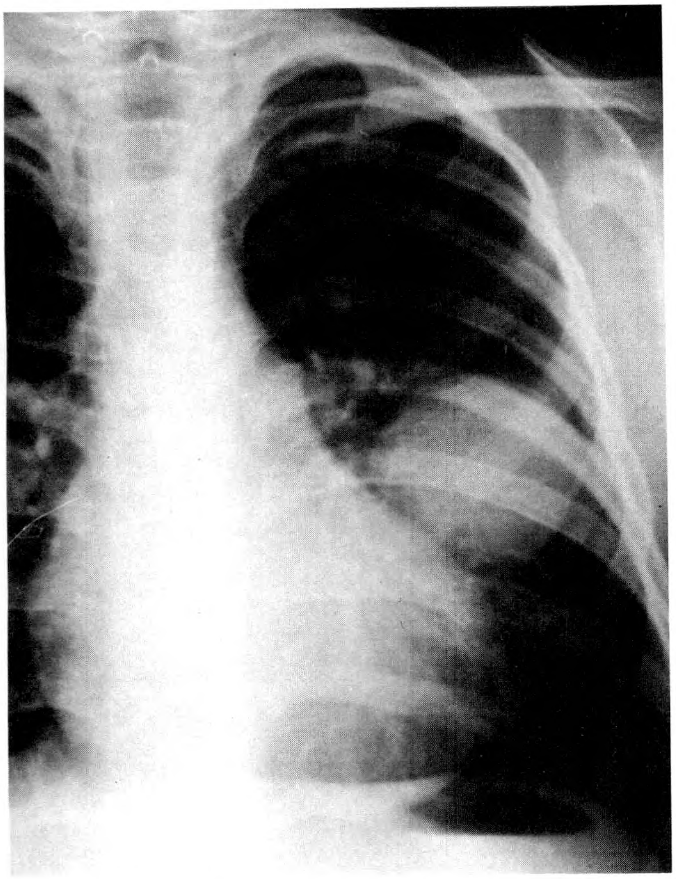


FIG. 2. Chest films of a 13-year-old boy from interior Alaska: A. a survey film showing a discrete asymptomatic lesion of the left mid-lung field.

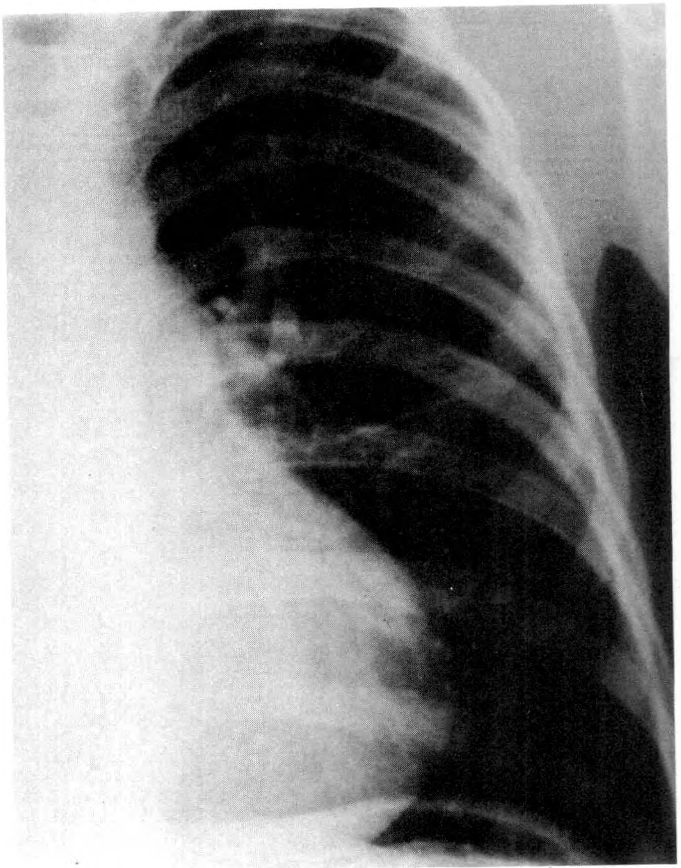


FIG. 2B. The next follow-up film of this patient showing that the cyst had disappeared. No symptoms were produced.

Although bronchiectasis has been associated with cystic hydatid disease[1,8,9,10] it has not, to our knowledge, been clearly documented as a cause of bronchiectasis. A preliminary review of bronchographic studies so far completed suggests that a causal relationship exists. Among the 30 patients with unruptured cysts, 10 had bronchography prior to the rupture of the cyst. No cyst-related bronchiectasis was observed in these patients. Of seven patients who had bronchography following rupture, six showed definite, though localized, bronchiectasis. In three patients, the bronchiectasis did not occur in the vicinity of the cyst, but was located in a different lobe in one, and in the contralateral lung in two. In two patients with bronchiectasis, both pre- and post-rupture bronchography was carried out. These radiograms demonstrated that the bronchiectasis developed following rupture of the cyst. It is tempting to speculate that the apparent development of bronchiectasis following spontaneous rupture of echinococcal cysts may partially account for the high rate of bronchiectasis observed in aboriginal populations in Alaska.[2,12] Clinical and laboratory studies designed to evaluate this possible relationship are in progress.

The occurrence of local infiltrates or pneumonitis in the area of ruptured or aspirated cyst and the high rate of localized bronchiectasis following rupture suggest that a considerable host-tissue reaction is evoked by leakage of cyst fluid. Nevertheless, symptoms generally are transient and would seem to be relatively insignificant in comparison to the risks and discomfort of a pulmonary resection.

The course of the disease in the 30 patients we have followed seems to warrant the conclusion that sylvatic cystic hydatid disease should be treated non-surgically in almost all instances. However, it is important to determine whether the type of cyst is sylvatic or pastoral in origin. The differential diagnosis is largely based on the patient's history (*i.e.* the source of the infection). If the patient is a native of Alaska or northern Canada where moose and caribou are hunted and if the patient has been associated with dogs, the sylvatic form is almost certainly present. If the patient has not lived in the north but has had contact with farm dogs, particularly sheep dogs, or is an immigrant from a known major endemic region the more virulent pastoral form should be suspected.[11]

Summary

The clinical follow-up of 30 patients with pulmonary cystic hydatid disease of the sylvatic form treated non-surgically is presented. Fifteen cysts proceeded to spontaneous rupture. The patients exhibited few symptoms after rupture of the cysts except transient mild pneumonitis. A preliminary review of limited bronchography studies demonstrates that in some patients localized bronchiectasis may develop, apparently as a result of rupture of echinococcus cysts. This experience supports the belief that the indigenous form of this disease does not require aggressive surgical management. It is important to differentiate between the two forms of *E. granulosus* because operation is seldom indicated in the sylvatic form indigenous to Alaska and Canada but is universally recommended in the classical European or pastoral form of cystic hydatid disease.

Acknowledgment

We wish to thank Dr. Robert Rausch whose basic understanding of Echinococcosis has provided guidance both to our management of this problem and in the preparation of this report. We would also like to express our appreciation to Mrs. Ursula Strash for valuable technical assistance.

References

1. Chrysospathis, P.: Echinococcus Cysts of the Lung. Dis. Chest, **49**:278, 1966.
2. Fleshman, J. K., Wilson, J. F. and Cohen, J. J.: Bronchiectasis in Alaska Native Children. Arch. Environ. Health, **17**:517, 1968.
3. Hurlburt, Ward B. and Wilson, J. F.: Cystic Hydatid Disease in Alaska. To be published in Proc. Clin. Soc. Commiss. Off. Assoc. USPHS.
4. Kagan, I. G., Osimani, J. J., Varela, J. C. and Allain, D. S.: Evaluation of Intradermal and Serologic Tests for the Diagnosis of Hydatid Disease. Amer. J. Trop. Med. Hyg., **15**:172, 1966.
5. Meltzer, H., Kovacs, L., Orford, T. and Matas, M.: Echinococcus in North American Indians and Eskimos. Can. Med. Assoc. J., **75**:121, 1956.
6. Schiller, E. L.: Echinococcus in North America. Ann. Intern. Med., **52**:464, 1960.
7. Schwabe, C. W.: Epidemiology of Echinococcosis. Bull. WHO., **39**:131, 1968.
8. Srouji, M., Mulhim, R. and Wilson, J. L.: Hydatid Cyst of the Lung with Bronchographic Evaluation of Treatment by Internal Suture of the Pericyst. J. Thorac. Surg., **35**:(6) 779, 1958.
9. Tsakayiannis, E., Pappis, C. and Moussatos, G.: Late Results of Conservative Surgical Procedures in Hydatid Disease of the Lung in Children. Surgery, **68**:379, 1970.
10. Waddle, N.: Pulmonary Hydatid Disease: A Review of 478 Cases Reported in the Louis Barnett Hydatid Registry of the Royal Australasian College of Surgeons. Aust. N. Z. J. Surg., **19**:273, 1950.
11. Wilson, J. F., Diddams, A. C. and Rausch, R. L.: Cystic Hydatid Disease in Alaska, A Review of 101 Autochthonous Cases of Echinococcus Granulosus Infection. Am. Rev. Resp. Dis., **98**:1968.
12. Wilson, J. F., Cohen, J. J. and Decker, A. M.: An Incidence Study of Bronchiectasis by Random Bronchography. Proc. Clin. Soc. Commiss. Off. Assoc. USPHS. 59, 1966.

First Rib Resection in the Treatment of Thoracic Outlet Syndrome:

Trabsaxillary and Posterior Thoracoplasty Approaches

D. K. ROEDER, CDR MC USN, M. MILLS, CAPT MC USN, J. J. McHALE, CAPT MC USN, B. M. SHEPARD, CDR MC USN, H. E. ASHWORTH, CDR MC USN

From the Department of Thoracic and Cardiovascular Surgery, Naval Hospital, National Naval Medical Center, Bethesda, Maryland

SIXTEEN YEARS have passed since Peet and associates[14] first noted the similarity between the many syndromes (Table 1) characterized by neurovascular compression symptoms of the upper extremity and suggested grouping them together as the *Thoracic Outlet Syndrome.* Ten years have elapsed since Clagett, in his Presidential Address before the American Association for Thoracic Surgery,[4] re-awakened interest in first rib resection in the treatment of thoracic outlet syndrome. Despite the unifying influence of these two works and a number of other excellent recent articles,[7,9,10,12,13,18,19,20] this subject remains an enigma to many physicians, and in the surgical literature, confusion over the approach to first rib resection remains.

The earliest reference to a patient with symptoms and signs compatible with thoracic outlet compression is in the third chapter of William Harvey's *de Motu Cordis.*[8] Although he believed his patient to have diminished distal blood flow in the involved arm due to "interception by aneurysm," he noted that "whenever the motion of the blood is impeded by compression. . . . there is less pulsation distally . . . ."[8] In 1821, Sir Astley Cooper described the symptoms of thoracic outlet compression:

> The subject of it was a woman who was admitted into Guy's Hospital having no pulse at the wrist or elbow. Her hand was of a venous redness, always cold, generally denumed, yet seemed painful; there were small gangrenous spots upon it . . . these appearances were found to be the consequence of a projection of the lower cervical vertebra towards the clavicle, and consequent pressure upon the subclavian artery.[5]

Forty years later, Coote[6] performed the first operative decompression with relief of symptoms. Numerous other papers document the history of the development of surgical technics and the shaping of medical thought regarding this entity. Thomas Murphy in 1910, first described the resection of a normal first rib with relief of symptoms of neurovascular compression.[11] Stopford and Telford[17] in 1919, favored first rib resection. In 1927, Brickner[2] also wrote of first rib resection but had the misfortune to have his article immediately follow Adson and Coffey's treatise[1] on the role of scalenotomy which, for so many years thereafter, was the preferred mode of therapy. Indeed, even today, references to this subject in the *Index Medicus* are recorded under the heading *Scalenus Anticus Syndrome.* In the 1940's, dissatisfaction with scalenotomy led to confusion. Many new syndromes were noted in the literature, and nonoperative treatment was recommended for most cases.

Based upon the work of many authors, but particularly Clagett[4] and Roos,[15,16] it is now apparent that first rib resection *is* the preferable mode of operative decompression of the thoracic outlet. In other words, the first rib is the common denominator to all forms of thoracic outlet compression. Most authorities[4,9,15,16,20] agree that ade-

---

Submitted for publication June 12, 1972.

Address Reprint Requests to: D. K. Roeder, Cdr MC USN Naval Hospital, Charleston, S. C. 29408.

The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

TABLE 1. *Partial Listing of the Entities Comprising the Thoracic Outlet Syndrome*

1. Cervical rib syndrome
2. Scalenus anticus syndrome
3. Brachiocephalic syndrome
4. Costoclavicular syndrome
5. Hyperabduction syndrome
6. Pectoralis minor syndrome
7. Humeral head syndrome
8. Nocturnal paresthetic brachialgia
9. Fractured clavicle syndrome
10. Effort vein thrombosis
11. Pneumatic hammer syndrome
12. Cervicobrachial neurovascular compression syndrome
13. First rib syndrome
14. Rucksack paralysis
15. Cervicothoracic outlet syndrome
16. Syndrome of the scalenus medius band

quate decompression cannot be attained with partial resection of the first rib. Therefore, any procedure for first rib resection must guarantee adequate exposure of the rib from costochondral junction to transverse process and must allow ample visualization of the adjacent neurovascular structures including the C_8 and T_1 nerve roots. In addition, it must be possible to remove a coexisting complete cervical rib when present through the same approach.

Upon review of the literature there appear to be two approaches which meet these criteria: the transaxillary approach (as described by Roos[15,16]) and the posterior thoracoplasty approach (as described by Clagett[4,9]). This report reviews a modest experience with 37 first rib resections in 34 patients over a period of 4 years, and compares our results using these two approaches to first rib resection. The period of follow-up has been 3½ years to 6 months. The patients have not been randomly selected.

Clinical Material

Of the 34 patients, 16 were male and 18 were female with an average age of 31.5 years (extremes of 16 and 51 years). Fourteen patients had arterial symptoms primarily. Three had venous symptoms primarily, and 17 had neurologic symptoms primarily. The major types of symptoms noted in this group are recorded in Table 2. One patient had chronic lymphedema of the arms secondary to old filariasis. In one patient a fractured clavicle immediately antedated the onset of symptoms. Of the 34 patients three had undergone previous cervical rib resection and three had undergone scalenotomy. One patient had undergone both a previous pectoralis minor section and a previous incomplete transaxillary first rib resection. One patient, a 23-year-old woman, had previously undergone two procedures for release of carpal tunnel syndrome, a scalenotomy, an attempted release of scar around the branchial plexus and subclavian vessels, and a transaxillary dorsal sympathectomy.

TABLE 2. *Symptoms in 34 Patients Undergoing Outlet Decompression*

Arterial	
Pallor, coolness	8
Tingling, numbness ("falls asleep")	18
Muscle fatigue, cramps	9
Raynaud-like phenomenon	2
Venous	
Swelling	8
Venous engorgement	4
Cyanosis	3
Neurologic	
Pain, paresthesias arm	13
forearm	14
hand	12
other (back, neck, shoulder)	4
Numbness, dysesthesia	14
Weakness	11
Atrophy	7

One-third of the patients engaged in activity or occupations requiring vigorous use of the upper extremities. In all patients the radial artery pulse could be obliterated upon assuming the 90° abduction and external rotation position (90° AER) of the affected upper extremity. In 19 patients (56%) bilateral findings were present with or without contralateral symptoms. In 30 patients (88%) a bruit was audible over the subclavian-axillary vessels with appropriate arm positioning. Muscle atrophy was noted in seven patients, involving the forearm and hand in three patients and the deltoid and pectoralis major in four patients. Subclavian arteriograms using the transfemoral Seldinger technic were positive in only one of the three instances in which they were performed. Venography was positive in the only two instances in which it was performed. Ulnar nerve conduction times were performed in 10 patients, being positive in only four instances. Interestingly, each of the patients in whom these studies were performed, despite the negative tests, fell into the good to excellent category of postoperative results.

Surgical results were classified according to the outline in Table 3. The major differential is between the good-excellent group and the fair-poor group. The former represent acceptable surgical results, while the latter do not, probably representing poor case selection.

Procedures

The first 13 patients underwent exploratory operation by the transaxillary approach. The next patient, who had undergone five previous operations, including two supraclavicular and one transaxillary procedures, was explored via the posterior thoracoplasty approach. Because of an exceedingly benign postoperative course in this patient, and because of some dissatisfaction with exposure using the transaxillary approach in obese and heavily muscled individuals, it was decided to compare the two procedures. Subsequently, 14 additional transaxillary first rib resections and 10 additional posterior thoracoplasty first rib resections have been performed.

Results

The surgical results, overall and comparison, and complications are recorded in Tables 4 and 5.

Posterior thoracoplasty group: Eleven posterior thoracoplasty first rib resections have been performed in ten patients. Three of these patients had noted recurrence of symptoms after having undergone previous (6 years, 3 years, and 6 months) cervical rib resection. One patient, a 38-year-old woman, had an arteriosclerotic plaque in the left subclavian artery proximal to the vertebral artery. She developed symptoms of subclavian steal on turning her head to the right. The radial pulse on the left demonstrated a marked pulse lag. On rising to 90° AER this pulse could be obliterated, as could the pulse on the unaffected, right side. First rib resection and interposition of a Dacron tube graft between the subclavian and axillary arteries were performed. She has had an excellent result after 18 months.

One patient, an obese 36-year-old woman who had undergone a previous transaxillary first rib resection at another hospital, noted recurrence of symptoms of venous compression. X-ray demonstrated an anterior rib segment remaining to the level of the scalene tubercle. This was resected and she has remained well during 12 months of follow-up.

There has been one complication in these 11 resections. A 20-year-old man developed a hematoma in the operative area and required transfusion (the only patient in the entire series who required blood replacement). The hematoma resolved spontaneously, and the patient when last seen was doing well.

One patient in the series underwent bilateral posterior thoracoplasty first rib resection, 5 months apart.

There have been excellent results in nine cases (82%), good in 1 (9%), and fair in 1 (9%) with follow-up for a period of 12 to 24 months. It is interesting that none of these patients have undergone the severe psychic and physcial trauma which have been ascribed to this procedure. The three most recent patients were discharged from the hospital on the fifth postoperative day and the majority have been able to resume normal activity within 6 weeks. One patient, a 27-year-old active duty Marine noted, however, that he is now limited to only 50 consecutive pushups because of "tiredness" in the back, whereas prior to the onset of symptoms (following a fractured clavicle) he could easily do twice that number.

TABLE 3. *Classification of Results*

Excellent	Asymptomatic.
Good	Improved, but with some residual symptoms, including intercostobrachial cutaneous nerve numbness.
Fair	Adequate decompression by presumptive testing, but little or no improvement in symptoms.
Poor	Symptomatically worse, or no improvement with inadequate decompression.

TABLE 4. *Results in 37 First Rib Resections*

	Overall	Transaxillary	Posterior Thoracoplasty
Excellent	24 (65%)	15 (58%)	9 (82%)
Good	10 (27%)	9 (35%)	1 (9%)
Fair	2 (5%)	1 (3%)	1 (9%)
Poor	1 (3%)	1 (3%)	0 (0%)

Transaxillary group: 26 transaxillary first rib resections have been performed in 24 patients. Three were performed in patients who had undergone previous scalenotomy.

There have been 15 (58%) excellent results, 9 (35%) good, 1 (3%) fair, and 1 (3%) poor. Two patients have complained of persistent intercostobrachial cutaneous nerve numbness. Both are more than 2 years postoperative and in neither was the intercostobrachial cutaneous nerve sacrificed. With that exception both would be classified as having had excellent results. In one patient, a pneumothorax was detected on the first postoperative day. He was treated by intercostal catheter drainage. His postoperative status has been unimproved and he has continued to complain of pain around the intercostal catheter site. He represents the one poor result in the series, and without question this instance is a case of improper selection. All of the complications noted in Table 5 occurred early in the series. Five patients in whom the pleural space was entered at operation required postoperative thoracentesis to drain serosanguineous fluid.

One patient, the first in the series, had an inadequate decompression of the posterior nerve roots with a 3 cm. posterior rib stump remaining. Although his symptoms were improved, he has continued to note mild arm and shoulder pain. He has refused further surgical exploration.

Discussion

The thoracic outlet syndrome is probably more common than is generally appreciated. It has been proven

TABLE 5. *Complications*

Transaxillary	
Seroma	1
Wound infection	1
Persistent Horner's syndrome	1
Pneumothorax	1
Annoying Intercostobrachial nerve numbness	2
Left lower lobe atelectasis	1
Posterior thoracoplasty	
Hematoma in area of rib resection	1

that many individuals have positive physical findings without significant symptoms.[21] It is not to be denied that many patients will be improved with a regimen of conservative treatment.[3,14] In this series the patients operated upon represent only 38% of the patients referred for evaluation of symptoms of thoracic outlet compression. With significant symptoms of venous, arterial, or neurologic compression, surgical decompression of the thoracic outlet is indicated. We have used purely symptomatic criteria in the selection of patients for surgical decompression. Presumptive testing (Adson test, Military maneuver, 90° AER, etc.) may be helpful, but a postive presumptive test alone is not an indication for surgical decompression. In our group of patients we have not been impressed that arteriography, venography, or ulnar nerve conduction times have helped to decide in favor of surgical decompression. This differs from other reported series, but thus far our results are no different (90% good-to-excellent).

Although the transaxillary approach to first rib resection has great cosmetic appeal, it has several drawbacks. It is not a procedure which lends itself well to teaching; it is not a procedure in which excellent exposure can be attained in all individuals; and it is not a procedure which can be performed without several assistants. In this series, there has not been a great deal of dissimilarity in the degree of discomfort or disability in patients operated upon via either the transaxillary or posterior thoracoplasty approach, despite the great difference in incision length and the obvious difference in muscle mass incised.

The transaxillary procedure is a better procedure by which to evaluate the entire thoracic outlet and to determine compression by the second thoracic rib as mentioned by Roos.[16] It can be performed more rapidly and with less blood loss than can the posterior thoracoplasty procedure. At present our operating time for the transaxillary procedure is 45–60 minutes, while for the posterior thoracoplasty procedure it is 90–105 minutes.

There is little question in our minds that it takes more experience to become technically proficient with the transaxillary procedure than with the posterior thoracoplasty procedure. Others have shared this view,[18] and the fact that complications have occurred more frequently early in various series bears this out. We believe that in the case of reoperation (except after previous scalenotomy), the posterior thoracoplasty approach is clearly superior, and that it is also superior in those individuals who are obese or heavily muscled.

It would appear that both methods of surgical decompression have a place in the treatment of the thoracic outlet syndrome. At present the necessity for individualization in the selection of patients for approach to surgical decompression based both upon the patient's body habitus and the surgeon's experience is justified.

Summary

A series of 37 first rib resections for decompression of the thoracic outlet is presented. Twenty-six first rib resections were performed by the transaxillary approach and 11 were performed by the posterior thoracoplasty approach. Results and complications are compared and the advantages and disadvantages of the two approaches are discussed.

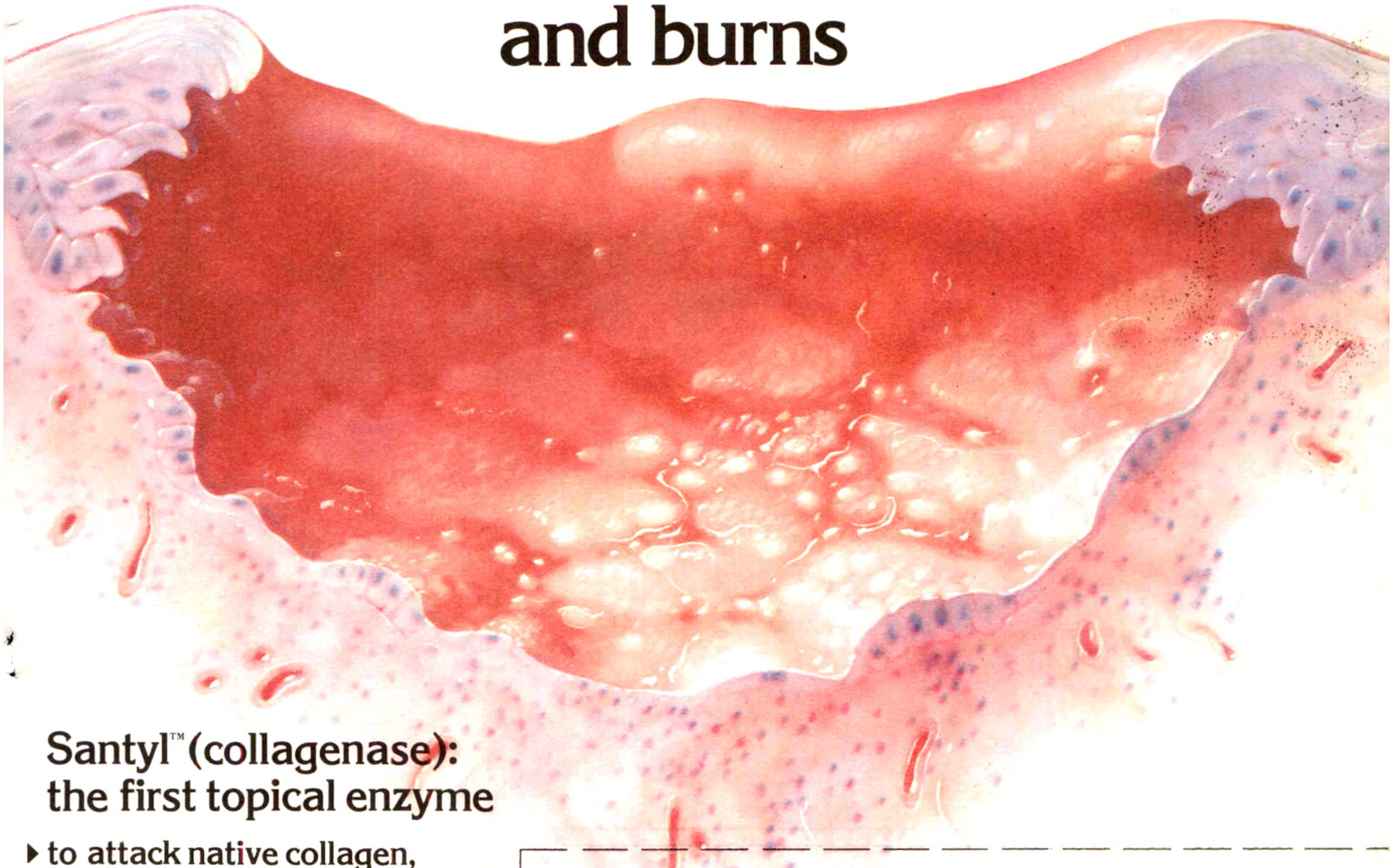
References

1. Adson, A. W. and Coffey, J. R.: Cervical Rib: A Method of Anterior Approach for Relief of Symptoms by Division of the Scalenus Anticus. Ann. Surg., **85**:839, 1927.
2. Brickner, W. M.: Brachial Plexus Pressure by the Normal First Rib. Ann. Surg., **85**:858, 1927.
3. Britt, L. P.: Non-operative Treatment of Thoracic Outlet Syndrome Symptoms. Clin. Orthop., **51**:45, 1967.
4. Clagett, O. T.: Presidential address: Research and Prosearch. J. Thorac. Cardiovasc. Surg., **44**:153, 1962.
5. Cooper, A.: On Exostosis, in Cooper, Cooper, and Travers: Surgical Essays, London, 3 ed., 1821, p. 128.
6. Coote, H.: Exostosis of the Left Transverse Process of the Seventh Cervical Vertebra Surrounded by Blood Vessels and Nerves: Successful Removal. Lancet, **1**:360, 1861.
7. Ferguson, T. B., Burford, T. H. and Roper, C. L.: Neurovascular Compression at the Superior Thoracic Aperture: Surgical Management. Ann. Surg., **167**:573, 1968.
8. Harvey, W.: Exercitatio anatomica de motu cordis et sanguinis in animalibus (1627), translated by C. D. Leake, Chas. C Thomas, Springfield, Illinois, 5 ed., 1970, p. 36.
9. Longo, M. F., Clagett, O. T. and Fairbairn, T. F.: Surgical Treatment of Thoracic Outlet Syndrome. Ann. Surg., **171**: 538, 1970.
10. Lord, J. W.: Thoracic Outlet Syndromes: Current Management. Ann. Surg., **173**:700, 1971.
11. Murphy, T.: Brachial Neuritis Caused by Pressure of First Rib. Aust. Med. J., **15**:582, 1910.
12. Nelson, R. M. and Davis, R. W.: Thoracic Outlet Compression Syndrome. Ann. Thorac. Surg., **8**:437, 1969.
13. Nelson, R. M. and Jenson, C. B.: Anterior Approach for Excision of the First Rib. Ann. Thorac. Surg., **9**:30, 1970.
14. Peet, R. M., Hendricksen, J. D., Guderson, T. P. and Martin, G. M.: Thoracic Outlet Syndrome: Evaluation of a Therapeutic Exercise Program. Proc. Mayo Clin., **31**:281, 1956.
15. Roos, D. B.: Transaxillary Approach for First Rib Resection to Relieve Thoracic Outlet Syndrome. Ann Surg., **163**:354, 1966.
16. Roos, D. B.: Experience with First Rib Resection for Thoracic Outlet Syndrome. Ann. Surg., **173**:429, 1971.
17. Stopford, J. S. B. and Telford, E. D.: Compression of the Lower Trunk of the Brachial Plexus by a First Dorsal Rib. Brit. J. Surg., **7**:168, 1919.
18. Taheri, S. A.: Present Status of Surgical Treatment of Thoracic Outlet Syndrome. Vascular Surg., **4**:217, 1970.
19. Tamvakopolous, S. K.: Thoracic Outlet Syndrome. Rev. Surg., **27**:8, 1970.
20. Urschel, H. C., Paulson, D. L. and McNamara, J. J.: Thoracic Outlet Syndrome. Ann. Thorac. Surg., **6**:1, 1968.
21. Wright, I. S.: The Neurovascular Syndrome Produced by Hyperabduction of the Arms. Am. Heart J., **29**:1, 1945.

new Santyl™ ointment (collagenase)

digests debris and the collagen that anchors it

A better beginning for the treatment of dermal ulcers and burns



Santyl™ (collagenase): the first topical enzyme

- **to attack native collagen,** a substance ordinarily resistant to all common proteolytic enzymes used in wound debridement
- **to digest denatured collagen,** the main constituent of dense burn eschar and necrotic debris that must often be removed before healing can take place
- **to dissolve collagenous strands** that "anchor" debris to the wound surface

Please provide additional scientific information on Santyl™ ointment (collagenase)

Name 1 2 3 4 5 6

Nursing home affiliation

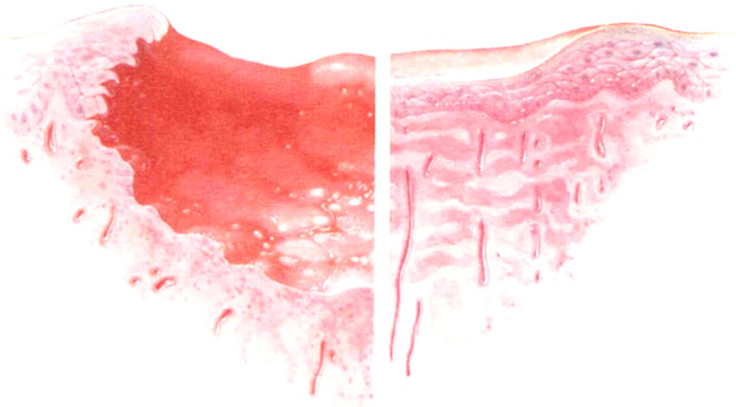
Hospital affiliation

Office address

Santyl™: new for dermal ulcers and burns

A cleaner base to build on promotes better healing in the end

Necrotic material is usually anchored to the wound surface by strands of undenatured collagen. Until these collagenous strands are severed, debridement is incomplete, granulation is slowed, and no supportive base is available for epithelization.[1]



Artist's conception of healing decubitus ulcer

With Santyl, debridement and subsequent healing have been reported to proceed rapidly.[1-3] A markedly reduced incidence of hypertrophic scarring reported with Santyl is believed to be due to the fact that epithelization proceeds from a completely debrided base.[1]

Indications: Santyl Ointment is indicated for debriding dermal ulcers and severely burned areas. In other types of necrotic skin lesions reports on the use of Santyl Ointment have been limited to clinical observations without controls.
Contraindications: Application is contraindicated in patients who have shown local or systemic hypersensitivity to Collagenase.

Precautions: The enzyme's optimal pH range is 7 to 8. Lower pH conditions have a definite adverse effect on the enzyme's activity, and appropriate precautions should be taken.

The enzymatic activity is also adversely affected by detergents and hexachlorophene and heavy metal ions such as mercury and silver which are used in some antiseptics. When it is suspected such materials have been used, the site should be carefully cleansed by repeated washings with normal saline before Santyl Ointment is applied. Soaks containing metal ions or acidic solutions such as Burow's solution should be avoided because of the metal ion and low pH. Cleansing materials such as hydrogen peroxide or Dakin's solution do not interfere with the activity of the enzyme.

Debilitated patients should be closely monitored for systemic bacterial infections because of the theoretical possibility that debriding enzymes may increase the risk of bacteremia.

The ointment should be confined to the area of the lesion in order to avoid the risk of irritation or maceration of normal skin.

A slight erythema has been noted occasionally in the surrounding tissue particularly when the enzyme ointment was not confined to the lesion. This can be readily controlled by protecting the healthy skin with a material such as Lassar's paste.

Since the enzyme is a protein, sensitization may develop with prolonged use although none has been observed to date.

Adverse Reactions: Adverse reactions to Collagenase have not been noted when used as directed.

Dosage & Administration: Santyl Ointment should be applied once daily (or once every other day in the case of outpatients) in the following manner.

(1) Prior to application the lesions should be gently cleansed with a gauze pad saturated in normal saline, buffer (pH 7.0-7.5) or hydrogen peroxide to remove any film and digested material.

(2) Whenever infection is present, as evidenced by positive cultures, pus, inflammation or odor, it is desirable to use an appropriate topical antibacterial agent. Neomycin-Bacitracin-Polymyxin B (Neosporin) has been found compatible with Santyl Ointment. This antibiotic should be applied to the lesion in powder form or solution prior to the application of Santyl Ointment. Should the infection not respond, therapy with Santyl Ointment should be discontinued until remission of the infection.

(3) Santyl Ointment should be applied (using a wooden tongue depressor or spatula) directly to deep wounds, or, when dealing with shallow wounds, to a sterile gauze pad which is then applied to wound. The wound is covered with sterile gauze pad and secured with clear tape or Kling bandage.

(4) Crosshatching thick eschar with a #11 blade is helpful. It is also desirable to remove as much loosened detritus as can be done readily with forceps and scissors.

(5) All excess ointment should be removed each time dressing is changed.

(6) Use of the ointment should be terminated when sufficient debridement of necrotic tissue has taken place.

Overdose: Action of the enzyme may be stopped, should this be desired, by the application of Burow's solution U.S.P. (pH 3.6-4.4) to the lesion.

How Supplied: Santyl Ointment contains 250 units of Collagenase enzyme per gram of white petrolatum U.S.P. The potency assay of Collagenase is based on the digestion of undenatured collagen (from bovine Achilles tendon) at pH 7.2 and 37°C. for 24 hours. The number of peptides cleaved are measured by reaction with ninhydrin. Peptides released by a trypsin digestion control are subtracted. One net Collagenase unit will solubilize ninhydrin reactive material equivalent to 4 micromoles of Leucine.

1. Boxer A M *et al*: *Geriatrics*, July 1969. **2.** Haimovici H and Strauch B: in Mandl Ines (ed): Collagenase, Gordon and Breach, New York, 1972, p. 177. **3.** Bardfeld L A: *op cit*, p. 191. **4.** Varma A O *et al*: *Surg. Gynec. Obstet.* *136*:281, Feb. 1973.

A free in-service educational program on the use of Santyl will be provided upon request.

First Class
Permit No. 528
Clifton
New Jersey 07012

BUSINESS REPLY MAIL

No postage stamp necessary if mailed in the United States

Postage will be paid by

Knoll Pharmaceutical Co.
30 North Jefferson Road
Whippany, New Jersey
07981

Santyl™
ointment
(collagenase)

"...because of its unique ability to hydrolyze native collagen, it may prove to be the drug of choice for wound debridement."[4]

KNOLL

Knoll Pharmaceutical Co.
30 North Jefferson Road
Whippany, New Jersey
07981

Icteric Thoracic Duct Lymph:

Significance in Patients With Manifestations of Obstructive Jaundice

ALLAN E. DUMONT, M.D.

From the Department of Surgery, New York University School of Medicine, New York City, 10016

In patients with clinical features of obstructive jaundice, a more complex mechanism than simple regurgitation of bile into the venous system may underlie hyperbilirubinemia. Some observations, including those of Saunders in 1795, suggest that bilirubin enters blood predominantly via liver lymphatics and the thoracic duct, while others indicate that this route is important, if at all, only in the first few hours of biliary obstruction.[3,4,6,8,9,14,15,19,20,21,27,29] An attempt to resolve this question and to clarify the origin of excess bilirubin in thoracic duct lymph forms the basis for this report. Based on the fact that patients with liver disease may display many of the biochemical and clinical features of "surgical jaundice", thoracic duct lymph, a more sensitive and dynamic guide to precise diagnosis than serum alone, was studied in 16 patients with clinical and laboratory manifestations of obstructive jaundice.[30]

Recent studies indicate that all of the bilirubin circulating in body fluids is bound to protein and therefore it no longer seems reasonable to consider mechanisms regulating entry of excess bilirubin into thoracic duct lymph and blood without considering the source and relative amounts of protein in these fluids.[2,7] It is recognized that protein concentration in liver lymph is practically identical with that of plasma while lymph from the less permeable extrahepatic portal bed contains less than half of this amount. Thoracic duct lymph/serum protein ratios were therefore used to calculate the proportions of thoracic duct lymph derived from liver and from the extrahepatic portal bed, together the source of almost all thoracic duct lymph.[31] A comparison between this ratio and that of bilirubin then provided information concerning the origin of bilirubin in lymph.

In addition, the old question of whether or not components of bile are transported to blood in significant amounts in thoracic duct lymph was re-examined by determining the effects of temporarily excluding icteric lymph from blood.

Clinical Data

Thoracic duct cannulation was performed in the neck under local anesthesia in 16 adult patients with clinical and laboratory manifestations of obstructive jaundice. Serum bilirubin levels ranged from 5 to 47 mg./100ml. and conjugated bilirubin was the predominant component in the serum of each patient. Jaundice had been present for variable periods of time although for not less than 2 weeks in any patient and was uniformly accompanied by clay colored stools and biliuria. In addition to examination of thoracic duct lymph, definitive diagnosis in some patients also required exploratory laparotomy and/or liver biopsy. Thus extrahepatic biliary obstruction due to carcinoma was eventually found in eight and of the remainder, five had intrahepatic cholestasis[18,24] (in one case due to Thorazine) and three had primary liver disease. Diagnostic aspects of the flow and composition of thoracic duct lymph (apart from bilirubin and protein levels) in some of these patients were considered in an earlier report.[30]

Cannulation was performed after an overnight fast and the initial lymph sample was taken for analysis within a few minutes of establishing flow through the cannula; simultaneously and at intervals thereafter samples of venous blood were obtained from an antecubital vein. When lymph drainage was continued for

---

Submitted for publication March 29, 1972.

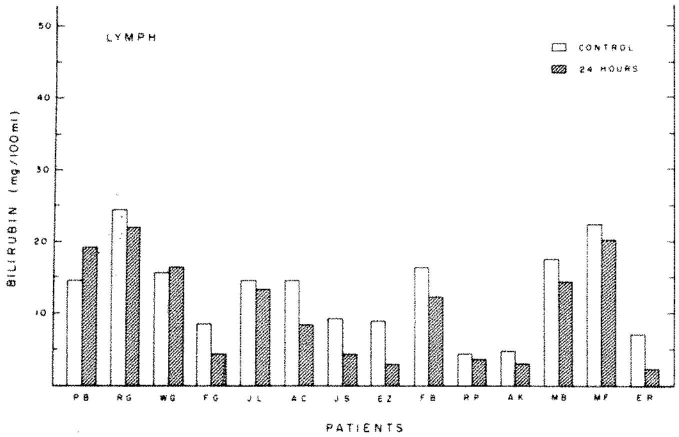


FIG. 1. Total bilirubin levels in samples of lymph (A) and serum (B) collected at the onset and after 24 hours of thoracic duct drainage.

more than a few hours, fluid and protein balance were carefully maintained by a combination of oral fat-free fluids and by intravenous replacement therapy with Ringer's lactate solution containing albumin.

Protein levels in lymph and serum were measured by the biuret method and bilirubin by the Van den Bergh technic.

Results

Lymph flow ranged from .2 to 3 cc./minute (normal 0.5 to 1.5). Lymph/serum bilirubin ratios ranged from 0.1 to 1 and averaged 0.6. Conjugated bilirubin was the principal component in serum and in lymph in each patient.

Lymph/serum bilirubin ratios were highest (0.8 or more) in two patients with primary liver disease, a patient with intrahepatic cholestasis (Thorazine jaundice) and a patient with extrahepatic biliary obstruction. These ratios were lowest (0.4 or less) in two patients with extrahepatic biliary obstruction and one with hepatocellular disease. Ratios in the middle range (0.5 to 0.7) were found in the remaining nine patients.

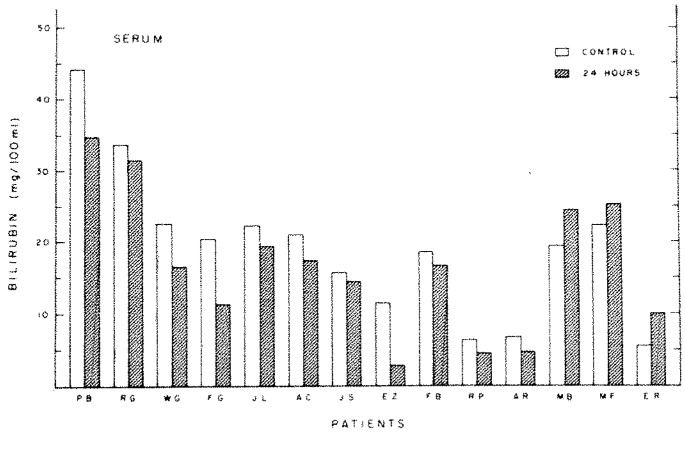


FIG. 1B. See legend for Figure 1.

Lymph/serum protein ratios were in the normal range of 0.5 to 0.55 in eight patients and of the remainder, five were lower and three higher. These variations appeared to bear no direct relationship to the type of underlying hepatic disorder.

When lymph drainage was continued in 14 patients (up to 4 days) lymph and serum bilirubin levels declined in 11, a decrease which averaged 5.1 mg. in serum in the first 24 hours (Figs. 1 A and B). Lymph levels usually declined at a slower rate. In the three patients in whom serum and lymph levels remained unchanged, intrahepatic cholestasis was diagnosed in two and hepatocellular disease in one. In four patients with intractable pruritus, two with extrahepatic biliary obstruction and two with intrahepatic cholestasis, itching stopped within a few hours of lymph drainage and then resumed following cessation of lymph flow.

Pertinent data from these patients are summarized in Table 1.

Discussion

All 16 patients included in this study fulfilled the conditions generally accepted for the diagnosis of obstructive jaundice. Regardless of the underlying condition whether an abnormally permeable or obstructed biliary system or primary liver disease, clinical manifestations were similar. In contrast, differences in lymph/serum protein and bilirubin ratios and in the relationship of one to the other were striking.

With respect to protein, three different patterns were recognized. First, in eight patients a normal ratio of 0.5 to 0.66 was found indicating that thoracic duct lymph derived normally in roughly equal amounts from liver and from the extrahepatic portal bed. Second, in three patients lymph/serum protein ratios exceeded 0.8 reflecting an abnormal preponderance of high protein liver lymph, the result usually of hepatic venous outflow obstruction. Third, in five patients lymph/serum protein ratios were 0.4 or less indicating that an abnormally large proportion of lymph derived from the extrahepatic portal bed, the result usually of impairment to flow in the portal vein. These variations in the lymph/serum protein ratio did not correlate with the distribution of bilirubin between thoracic duct lymph and serum.

An explanation of differences between lymph/serum protein ratios on the one hand and those of bilirubin on the other was sought with several possibilities in mind. First, bilirubin could enter lymph in liver and in the extrahepatic portal bed exclusively by transfer from plasma across the capillary wall. In this case all of the bilirubin entering lymph from plasma would be protein

TABLE 1. *Clinical and Laboratory Data in 16 Patients with Manifestations of Obstructive Jaundice*

Patient	Diagnosis	Lymph Flow Rate (cc/min)	Days Drained	L/S Prot.*	Prot. Ratio	L/S Bil.†	Bil. Ratio	L/S Dir.	L/S Ind.	24 Hours			Last Day		
										Total	Dir.	Ind.	Total	Dir.	Ind.
A.K.	recurrent cholestasis	3	3	3.5/5.4	0.6	4.8/6.9	0.6	4/4.6	.7/2.3	3/4.8	2.3/3.1	7/1.7	2.5/3.6	1.5/2.4	1/1.6
J.L.	liver disease	2	4	3.5/6.5	0.5	14.6/23.2	0.6	10.2/18	4.4/5.2	13.1/19.4	7.1/11.2	7/8.2	11.2/12.6	5.1/10.2	6.1/2.4
M.B.	thorazine jaundice	2.3	2	5/7.1	0.6	17.4/19.4	0.8	12.9/16.3	4.5/3.1	14.2/24.2	12.9/18.5	1.3/5.7	15.2/18.6	10.5/13.1	4.7/7.5
F.W.	extrahepatic obstruction	2	1	3.9/6.4	0.6	38.4/47.4	0.8	27.3/31.3	11.1/16.1						
F.G.	extrahepatic obstruction	0.8	1	3.5/6.6	0.5	8.6/20.4	0.4	4.7/13.6	3.9/6.8	4.4/11.2	2.1/4.1	2.3/7.1			
E.R.	liver disease	0.7	1	3/6.5	0.3	.7/5.6	0.1	.3/2.7	.3/2.8	2.1/10	1.3/5.9	.7/4			
R.G.	extrahepatic obstruction	0.2	1	4.3/6.9	0.6	24.3/33.6	0.6	19.8/26.5	4.4/7.1	22/31.4	17.4/24.4	4/7			
A.C.	extrahepatic obstruction	1	1	2.6/5.5	0.4	14.6/21	0.6	9/12.2	5.6/8.8	8.4/17.4	5.3/10.8	3.1/5.6			
P.B.	extrahepatic obstruction	1.5	4	2.3/6.6	0.3	14.6/43.2	0.3	11.9/27.3	2.6/15.9	19.2/34.8	12.2/27.3	7/7.5	62/19.8	1/14.4	5.1/5.3
E.Z.	cholestasis	1.5	3	6.6/7.5	0.8	9/11.5	0.7	5.5/4.8	3.4/6.7	3/2.8	2.2/2.3	1/.5	3/2.2	2/1.2	1.5/1.2
W.G.	cholestasis	1	2	3.6/3.9	0.9	15.7/23.7	0.6	11.5/14.5	4.2/9.2	16.3/16.5	10.5/12.9	5.8/3.4	15.7/15.7	9.2/8.4	6.4/7.3
R.P.	cholestasis	2	2	3/6.2	0.5	4.4/6.4	0.6	2.4/3.6	2/3.1	3.6/4.4	1.7/2.3	1.8/2.1	1.2/3.2	.8/1.8	.3/1.3
J.S.	extrahepatic obstruction	0.3	4	2.8/5.7	0.4	9.2/15.8	0.5	5.4/7.5	3.8/7.9	4.4/14.4	2.5/7.6	1.9/6.8	3.3/15	2.3/7.8	1.5/7.3
M.F.	extrahepatic obstruction	1	1	3.5/3.5	1	22.3/22.3	1	15.2/15.6	7.1/6.8	20.1/25.7	14.4/20.4	5.6/4.8			
F.B.	liver disease	1	1	2.1/4.6	0.5	16.3/18.6	0.8	10.6/15.4	5.6/3.1	12.1/16.8	8.5/13.2	3.5/3.5			
R.D.	extrahepatic obstruction	1	1	3.3/8	0.4	39.6/43.2	0.9	27.3/30.4	12.3/12.8						

* Lymph/Serum protein ratio in grams per 100 ml

† Lymph/Serum bilirubin ratio in mg per 100 ml

Dir. = Direct reacting bilirubin

Ind. = Subdirect reacting bilirubin

bound and lymph/serum ratios of bilirubin and protein would thus be similar if not identical. Second, additional amounts of bilirubin could enter liver lymph independently of protein by direct transfer from hepatocytes or leaky canaliculi. In this event lymph/serum bilirubin ratios would be higher than those of protein. Third, an increasing amount of bilirubin filtering across the sinusoid could be cleared from hepatic lymph as biliary secretory function returned. The net result of this process would be lymph/serum bilirubin ratios lower than those of protein.

Based on these considerations it is evident that bilirubin entered lymph by direct transfer from plasma alone in nine patients. In five others, including the four with the highest lymph/serum bilirubin ratios, bilirubin was added to hepatic lymph from hepatocytes or leaky canaliculi. The results in this latter group are of particular interest as they tend to confirm a direct functional pathway from the biliary secretory unit to hepatic lymph, a route previously rejected by some investigators while supported by others.[23,29] In this regard, evidence obtained recently from electron photomicrographs indicates that hepatic cells and canaliculi have access to blood in sinusoids solely through an intercellular space which communicates with the perisinusoidal space of Disse, the major source of hepatic lymph.[11] Evidence favoring the view that bilirubin is added to liver lymph from hepatocytes rather than canaliculi has been reviewed by others.[13]

Lymph/serum bilirubin ratios were significantly less than those of protein in only two patients. Primary liver disease was diagnosed in one who also demonstrated the lowest lymph/serum bilirubin ratio; intrahepatic cholestasis was diagnosed in the other, in whom serum bilirubin levels continued to decline after removal of the cannula.

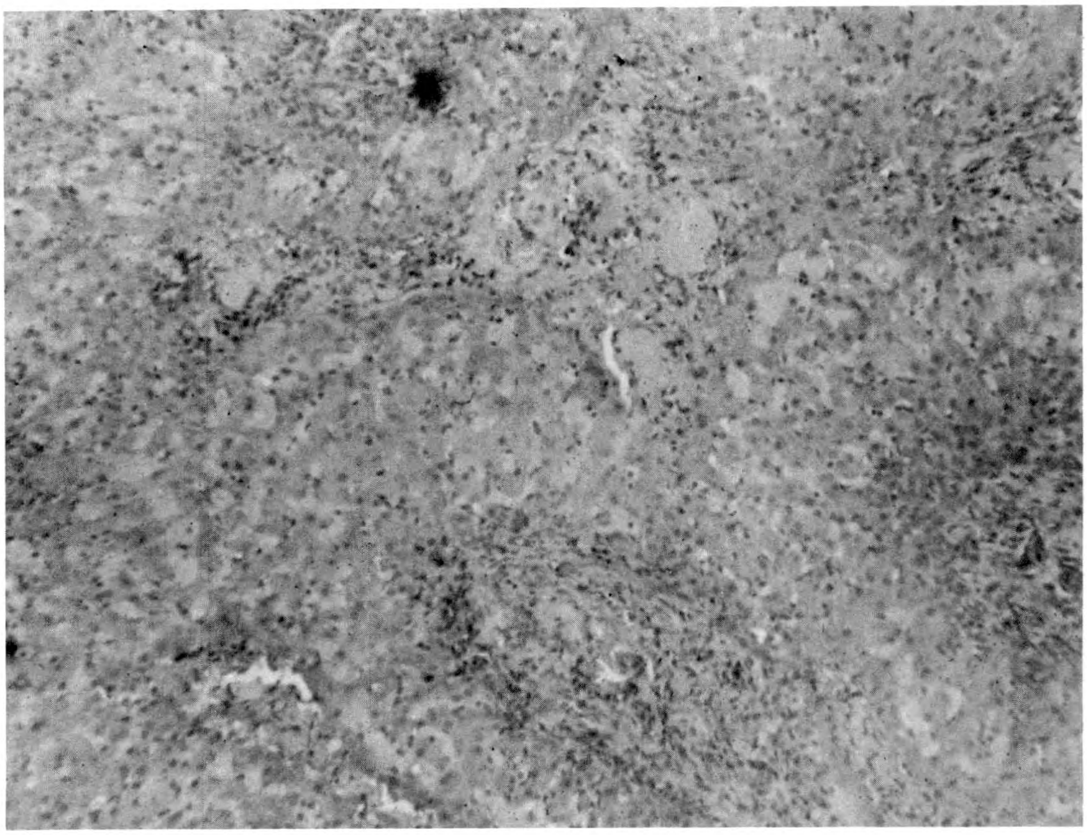
The reserve capacity of protein to bind bilirubin (up to 60 mg. of bilirubin per 6–7 Gm. of protein) is such that it might be possible, on a theoretical basis, for thoracic duct lymph levels of total blirubin to exceed those in serum, even in patients in whom lymph/serum protein ratios are normal. Although concentrations of either conjugated or unconjugated components in thoracic duct lymph did at times exceed levels of the corresponding component in serum in a few patients, this was never the case for total bilirubin levels. For the latter to be higher in thoracic duct lymph than in serum selective entry into liver lymph of both components in large amounts would probably be required.

Decrease in serum bilirubin levels observed in the majority of patients in whom lymph was continuously diverted from blood signifies that bilirubin entering blood in thoracic duct lymph accounts for a significant component of circulating bilirubin. As approximately one half of the circulating pool of plasma protein is transported in thoracic duct lymph each 24 hours, it seems likely by analogy that when lymph/serum ratios of bilirubin equal or exceed those of protein, at least half of the circulating pool of bilirubin also enters blood via thoracic duct lymph each 24 hours. The finding that ratios of conjugated to unconjugated bilirubin in thoracic duct lymph differ at times from those in serum in no way alters this concept. Such differences could result from selected urinary excretion of conjugated bilirubin and from extrahepatic deconjugation of circulating bilirubin.[1] Even in the absence of any specific contribution of bilirubin to hepatic lymph from hepatocytes or canaliculi, continuous transfer into liver and extrahepatic lymph from plasma is in itself sufficient to insure a high lymph/serum ratio. Further, as the data failed to disclose any correlation between levels of excess bilirubin in serum and lymph/serum ratios, explanations of jaundice which relate degree of hyperbilirubinemia to diffusion of bilirubin into tissues should be discarded.

Data obtained in two of the patients in this study may warrant special comment. A diagnosis of intrahepatic cholestasis due to thorazine ingestion[5,10,12] in one and of benign recurrent cholestasis[22,16] in the other were made respectively several weeks and 10 years after cannulation. In the first patient conjugated bilirubin was added to liver lymph from an intrahepatic source other than plasma. After 2 days of lymph drainage levels of conjugated bilirubin fell in both lymph and serum while those of the unconjugated component doubled in serum and remained unchanged in lymph. Although the significance of these findings is still obscure the data suggest that unconjugated bilirubin selectively entered hepatic venous blood. In the second patient lymph/serum ratios of bilirubin equaled those of protein and serum levels decreased by one half after 3 days of lymph drainage.

A finding that previously intractable pruritus ceased within a few hours of diverting lymph from blood suggests that thoracic duct lymph is an important link in the recirculation of bile salts. As recent studies suggest that hepatic bile salt production stops within a short time after bile flow is obstructed[25] it is likely that lymph borne bile salts derive predominantly from plasma. Support for the view that bile salts recirculate in thoracic duct lymph was also provided by results of other studies which demonstrated that inflammation in livers of animals with experimentally produced biliary obstruction decreased markedly following anastomosis of the thoracic duct to the esophagus (Figs. 2 A and B). Persistently elevated titers of circulating bile salts rather than simple hepatic retention may in fact underlie the hepatic inflammatory lesion.[17] Clinical attempts to drain icteric hepatic or thoracic duct lymph into the

FIG. 2. Histologic appearance of the liver in a dog after 3 weeks of extrahepatic biliary obstruction (A) and then 4 weeks later (B). In the interval between these open liver biopsies, icteric thoracic duct lymph was continuously diverted away from blood and into the cervical esophagus. Disappearance of bile "lakes", decrease in accumulation of inflammatory cells and partial restoration of normal cords of liver cells is evident even though extrahepatic biliary obstruction persists (H.&E. ×100).



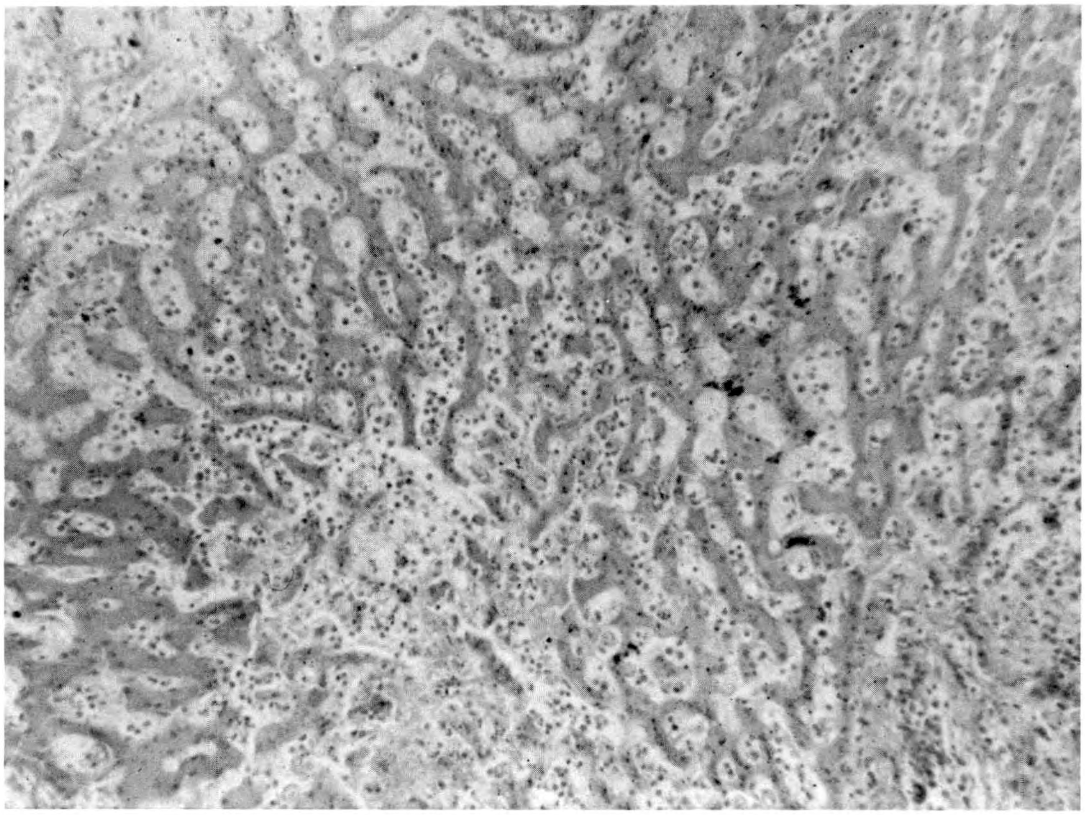


FIG. 2B. See legend for Figure 2.

gastrointestinal tract and away from blood thus appear to have a rational basis.[16,28]

Summary

Levels of bilirubin and protein were measured in thoracic duct lymph and in serum in 16 patients with clinical manifestations of obstructive jaundice. In contrast to the similarity of the clinical picture several strikingly different patterns in the relationship between lymph/serum bilirubin and protein ratios were identified. Based on the consideration that bilirubin circulates in body fluids in a protein bound form, the results suggest that in nine patients excess bilirubin filtered continuously from blood to lymph across capillary walls in the liver and extrahepatic portal bed. In five others additional bilirubin entered hepatic lymph from either hepatocytes or leaky canaliculi. In the remaining two patients significant amounts of recirculating bilirubin apparently were cleared from hepatic lymph as biliary secretory function returned. Levels of circulating bilirubin decreased in 11 of 14 patients following diversion of thoracic duct lymph from blood, indicating that a significant component and perhaps one half of the excess circulating bilirubin pool normally entered blood via the thoracic duct each 24 hours. As the degree of hyperbilirubinemia bore no relationship to lymph/serum bilirubin ratios, explanations of jaundice which relate diffusion into tissue to degree of hyperbilirubinemia are incorrect and should be discarded. Cessation of pruritus following diversion of lymph noted in four of these patients suggests that excess bile salts also recirculate to the blood via lymph.

References

1. Acocella, G., Tenconi, L. T., Armas-Merino, R., Raia, S. and Billing, B. H.: Does Deconjugation of Bilirubin Glucuronide Occur in Obstructive Jaundice? Lancet, 1:68, 1968.
2. Billing, B. H.: The Disposal of Bilirubin. In Progress in Liver Diseases II H. Popper and F. Schaffner, Eds. Grune and Stratton, 1965, pp. 1–14.
3. Bloom, W.: Role of Lymphatics in Absorption of Bile Pigment from Liver in Early Obstructive Jaundice. Bull. Johns Hopkins Hosp., 34:316, 1923.
4. Carlesten, A., Edlund, Y. and Thulesius, O.: Bilirubin, Alkaline Phosphatase and Transaminases in Blood and Lymph During Biliary Obstruction in the Cat. Acta. Physiol. Scand., 53:58, 1961.
5. Cohen, I. M. and Archer, J. D.: Liver Function and Hepatic Complications in Patients Receiving Chlorpromazine. JAMA, 159:99, 1955.
6. Dumont, A. E., Doubilet, H., Witte, C. L. and Mulholland, J. H.: Disorders of the Biliary-Pancreatic System: Observations on Lymph Drainage in Jaundiced Patients. Ann. Surg., 153:774, 1961.
7. Fosgren, L.: Observations on the Chemical Composition of the Thoracic Duct Lymph in Patients with Biliary Obstruction. Acta. Chir. Scand., 135:559, 1969.
8. Gonzalez-Oddone, M. V.: Bilirubin, Bromsulfalein, Bile Acids, Alkaline Phosphatase and Cholesterol of Thoracic Duct Lymph in Experimental Regurgitation Jaundice. Proc. Soc. Exp. Biol. Med., 63:144, 1946.
9. Hanzon, V.: Liver Cell Secretion Under Normal and Pathologic Conditions Studied by Fluorescence Microscopy on Living Rats. Acta. Physiol. Scand., 28:Supp. 101, 1952.
10. Hargreaves, T.: Cholestatic Drugs and Bilirubin Metabolism. Nature, 206:154, 1965.
11. Heath, T. and Wissig, S. L.: The Fine Structure of Mouse Hepatic Cells. Am. J. Anat., 119:97, 1966.
12. Hoffbauer, F. W.: Clinical Aspects of Jaundice Resulting From Intrahepatic Obstruction. JAMA, 169:1453, 1959.
13. Krebs, J. S., Brauer, R. W., Bollman, J. and Leong, G. F.: Formation of Hepatic Lymph. Am. J. Physiol., 207:877, 1964.
14. Mallet-Guy, P., Michoulier, J. and Baer, S.: Experimental Studies on Liver Lymph Flow. Conditions Affecting Bilio-Lymphatic Transfer. *In* The Biliary System. W. Taylor, Ed. F. A. Davis Co., 1965, pp. 69–78.
15. Mayo, C. II and Greene, C. H.: Studies in the Metabolism of Bile. Am. J. Physiol., 89:280, 1929.
16. Miller, S., Fonkalsrud, E. W. and Longmire, W. P.: Current Concepts in the Management of Congenital Biliary Atresia. Arch. Surg., 92:813, 1966.
17. Moore, R. A.: Effect of Parabiosis on the Hepatic Changes Following Obstruction of the Common Bile Duct in Rats. Arch. Pathol., 34:196, 1942.
18. Popper, H. and Schaffner, F.: Pathology of Jaundice Resulting from Intrahepatic Cholestasis. JAMA, 169:1447, 1959.
19. Ritchie, H. D., Grindlay, J. H. and Bollman, J. L.: Surgical Jaundice: Experimental Evidence Against the Regurgitation Theory. Surg. Forum, 7:415, 1956.
20. Saunders, W. A.: Treatise on the Structure, Economy and Diseases of the Liver: Together with an Inquiry Into the Properties and Component Parts of the Bile and Biliary Concretions. 3rd ed. W. Phillips, 1803, p. 111.
21. Shafiroff, B. G. P., Doubilet, H. and Ruggiero, W.: Bilirubin Resorption in Obstructive Jaundice. Proc. Soc. Exp. Biol. Med., 42:203, 1939.
22. Schapiro, R. H. and Isselbacher, K. J.: Benign Recurrent Intrahepatic Cholestasis. N. Engl. J. Med., 268:708, 1963.
23. Sherlock, S.: Biliary Secretory Failure in Man: The Problem of Cholestasis. *In* The Biliary System, W. Taylor, Ed. F. A. Davis Co. 1965, pp. 585–597.
24. Ibid.
25. Strasberg, S. M., Dorn, B. C., Small, D. M. and Egdahl, R. H.: The Effect of Biliary Tract Pressure on Bile Flow, Bile Salt Secretion and Bile Salt Synthesis in the Primate. Surgery, 70:140, 1971.
26. Summerskill, W. H. J. and Walshe, J. M.: Benign Recurrent Intrahepatic "Obstructive" Jaundice. Lancet, 2:686, 1959.
27. Whipple, G. H. and King, W.: The Pathogenesis of Icterus. J. Exp. Med., 13:115, 1911.
28. Williams, L. F. and Dooling, J. A.: Thoracic Duct Esophagus Anastomosis For Relief of Congenital Biliary Atresia. Surg. Forum, 14:189, 1963.
29. Witte, M. H., Dumont, A. E., Levine, N. and Cole, W. R.: Patterns of Distribution of Sulfobromophthalein in Lymph and Blood During Obstruction To Bile Flow. Am. J. Surg., 115:69, 1968.
30. Witte, M. H., Cole, W. R., Burton, D. F., Alvarez, L. and Dumont, A. E.: Thoracic Duct Cannulation and Differential Diagnosis of Obstructive Jaundice. JAMA, 204:366, 1968.
31. Witte, C. L., Witte, M. H., Dumont, A. E., Frist, J. and Cole, W. R.: Lymph Protein in Hepatic Cirrhosis and Experimental Hepatic and Portal Venous Hypertension. Ann. Surg., 168:567, 1968.

Humoral Recognition Deficiency in the Etiology of Reticuloendothelial Depression Induced by Surgery

WILLIAM A. SCOVILL, M.D.,* THOMAS M. SABA, PH.D.

Departments of Physiology and Surgery, University of Illinois, College of Medicine, Chicago, Illinois

THE RETICULOENDOTHELIAL (RE) or macrophage system represents a collection of mesenchymal derived cells which have the capacity to rapidly recognize and phagocytize denatured proteins, damaged autologus tissue and foreign particulate matter. A major portion of the RES consists of sessile macrophages localized in the liver, lungs, spleen and bone marrow.[2,3,35] Their distribution in relationship to the circulation, coupled with their phagocytic capacity allows them to monitor the blood and rapidly remove circulating foreign particulate antigens and degenerate endogenous tissue debris.[35] The immunologic and homeostatic role of this phagocytic clearance mechanism relative to both nonspecific and specific host-defense has been well documented.[2,3,4,11,26,35]

Experimental and clinical findings have demonstrated that macrophages are a major component of the host response associated with tumor growth,[28,39,43] bacterial infection[26,40] and diseases of altered immunity.[41] The importance of these findings relative to the concept of the RES as a defense apparatus are further emphasized by the observations that R.E. stimulation will protect against experimentally induced infections,[23] as well as lead to a regression of experimentally induced tumors.[8,29] Conversely, RE depression will enhance host susceptibility to tumor growth[3,4,35] and spread and decrease resistance to experimental bacterial infection.[3,26]

It has become increasingly evident that macrophage phagocytosis is intimately associated with humoral and cellular recognition mechanisms.[5,30,35] In this regard, macrophages can discriminate foreign matter and effete endogenous matter from healthy indigenous tissue. This capacity to discriminate "self" and "altered-self" appears to be related to the presence of specific plasma or serum proteins called "opsonins" or humoral recognition factors[5,9,23,30,35,38] which interact with the foreign or denatured surface and stimulate phagocytosis. Opsonin or humoral recognition factor[30,36] appears to be an alpha-2-globulin and its regulatory influence on phagocytosis has been recently quantified in this laboratory with isolated and purified opsonic protein.[1] The dependence of RE cell phagocytosis on opsonic activity has been demonstrated *in vivo*,[36] by the perfused liver,[15] by isolated liver slices,[38] and with isolated macrophage preparations.[9,31]

Several studies have directed attention to a possible functional relationship between operative stress and decreased resistance to the growth and spread of tumors.[17,19,25] Surgical trauma has been suggested by Gordon-Taylor[19] to induce an increased growth and spread of neoplastic disease during the postoperative period. El Rifi *et al.*[14] have correlated the decreased resistance of the postoperative period with an increased incidence of pulmonary metastasis. These findings, in addition to the effect of laparotomy[6] and hepatic surgery[16] as related to either tumor cell "takes" or tumor growth, provide support for the concept of altered host defense during the postoperative period.

Since the RES is a major mechanism of host resistance, and since surgical stress initiates a state of diminished host resistance, recent studies have focused attention on

---

Submitted for publication May 1, 1972.

Request reprints: Dr. Thomas M. Saba, Professor and Chairman, Department of Physiology, Albany Medical College, Albany, New York 12208.

This research was supported by the United States Public Health Service Grant AM 14382-02 from the National Institute of Arthritis and Metabolic Diseases.

[*] William A. Scovill, M.D., is a research fellow in the Department of Physiology, resident in the Department of Surgery, and a candidate for a M.S. degree in Surgery.

the effect of operation on the functional ability of the RES. In this regard, surgical manipulation of humans[13] and animals[33,34,37] will induce a significant alteration of RE function as evidenced by delayed blood clearance and decreased hepatic uptake of intravenously injected foreign particulate matter. This response does not seem to be related to a specific trauma model in that depression of the systemic clearance capacity of the RES has been noted in association with extra corporeal circulation[44] cutaneous burns[24,27,32] ligation of the superior mesenteric artery following laparotomy[22] and skin transplantation.[20] In view of the importance of opsonic or recognition factors in RE function,[30,35] the possibility exists that phagocytic depression following these various surgical and experimental procedures has a common etiologic mechanism, *i.e.*, deficiency of the opsonic or humoral recognition system.[34,35]

In the present investigation the phagocytic capacity of the RES was evaluated relative to the circulating level of plasma opsonic or recognition factor[30,35,38] activity both during and following major abdominal surgery in dogs. Since the major organ involved in the clearance is the liver, and since previous findings[13] suggest a potential role for hepatic blood flow alteration in the postoperative clearance response, the hepatic sinusoidal blood flow was also investigated as a potential factor mediating phagocytic changes during operation.

Materials and Methods

Healthy (12 hr. fasted) mongrel dogs weighing 13–18 Kg. and maintained in the Medical Research Laboratory Hospital were used in all experiments. Control, nonsurgically stressed dogs, and surgically stressed dogs were anesthetized with sodium pentobarbital (30 mg./Kg.) and allowed to breathe spontaneously via a cuffed endotracheal tube throughout the experimental period. The operative procedure employed was a standard right hemicolectomy with ileo-transverse colostomy which was performed over a 3-hr. period of time under sterile conditions.

RE phagocytic function was evaluated by means of the colloid clearance technic.[2,4,7] This method is based on the ability of fixed RE cells to phagocytically remove intravenously injected colloidal or particulate material,[35] and has been used extensively in animal[2,11,22,36] and human[39,40,41] studies. The test colloid employed was a radioiodinated lipid emulsion[10,36,40] referred to as the gelatinized^{131} I "RE test lipid emulsion."[7,36,38] This emulsion is prepared as an anhydrous base with glycerol,^{131} I triolein (Mallinkcrodt, St. Louis, Mo.) and soya lecithin mixed in a ratio of 10:10:1 by weight, respectively.[10] Prior to injection a 0.3% gelatin supplemented sterile 5% dextrose in water solution, adjusted to a pH of 7.4, was added to the anhydrous lipid base to provide an emulsion with a 20% base concentration.[7] The emulsion preparation was incubated at 37C for 20 min. prior to intravenous injection in order to affect gelatinization. This emulsion is exclusively removed from the vascular compartment by RE cells, especially the hepatic Kupffer cells[7,10,36] as confirmed by electronmicroscopy.[40]

The rate of vascular clearance of the radioiodinated lipid emulsion in dogs was used as a measure of RE phagocytic activity.[7,11,36] The radioactive emulsion with a specific activity of 0.01 μc./mg. was injected intravenously at a dose of 700 mg./Kg. body weight and serial 1.0 ml. timed arterial blood samples were taken every 2 min. for 14 min. from an indwelling femoral arterial polyethylene catheter (PE 260). The samples were analyzed for colloid concentration by radioassay in a Nuclear Chicago Auto-Gamma crystal scintillation system (Nuclear-Chicago, Desplaines, Ill.) as previously described.[7,36] The post-injection blood levels of colloid remaining in the vascular space at the varying time intervals following injection were expressed as the percent of the injected dose circulating per 100 ml. whole blood (%ID/100 ml.). This level of colloid retention was plotted semilogarithmically against time in min. and the phagocytic index K or the half-time ($t\frac{1}{2}$) for the vascular clearance of test colloid was determined.[7] The phagocytic index K was calculated from the expression:

$$K = \frac{\log C_1 - \log C_2,}{T_2 - T_1}$$

where, C_1 and C_2 represent the blood concentration at time T_1 and T_2, respectively.[2,3,35]

The opsonic or humoral recognition factor (HRF) activity of plasma,[30,36,38] before, during and after operation was determined using an *in vitro* bioassay technic.[30,36,38] This method has been extensively employed in the evaluation of opsonic or humoral recognition factor (HRF) activity in animals[36,38] and humans[9,30] under a variety of experimental conditions.[35] Briefly, liver slices weighing 200–400 mg. and 0.5 mm. in thickness were prepared from livers of normal rats using a Stadie-Riggs tissue slicer. The liver slices were incubated in a medium containing 1 ml. of experimental plasma, 2 ml. of Krebs Ringer phosphate buffered to pH 7.4, 100 USP units heparin (UpJohn, Kalamazoo, Michigan), and 2 mg. of the gelatinized^{131} I "RE test emulsion" (1% emulsion with 0.1% gelatin). All samples were incubated under a gas phase of 95% O_2 and 5% CO_2 in a Dubnoff metabolic shaker at 37C for 30 min. Following incubation, the tissue slices were washed, weighed and analyzed for colloid uptake. The opsonic or HRF activity of plasma was evaluated in terms of its ability to stimulate Kupffer cell phagocytosis, expressed as μg of the test colloid or per cent of the injected dose phagocytized per 100 mg. of liver tissue (μg/100 mg. or %ID/100 mg.).

The rate of blood clearance of previously opsonized test particles[36] was also evaluated in an attempt to demonstrate the reversability of any potential RE clearance depression due to deficiency of circulating opsonic or HRF activity. Opsonization of the test colloid was accomplished by incubation with normal heparinized plasma (200 mg./ml.) at 37C in a Dubnoff metabolic shaker for 15 min. as previously described.[36] The opsonized test colloid was injected intravenously (700 mg./Kg.) at the time of maximum RE phagocytic depression and its rate of clearance from the vascular space was evaluated in relationship to the clearance of an identical dose of the colloid in a non-opsonized form.

Hepatic blood flow was determined using an isotopic fractional clearance rate (k) technic.[3,12] A tracer dose of colloidal gold (^{198}Au-Abbott Lab, Chicago), below the critical colloid dose, equivalent to 50 μg/Kg. BW and having a specific activity 0.1 μc/μg gold was employed. At this dose, the rate limiting factor for the vascular clearance of the test colloid is hepatic sinusoidal blood flow and not RE phagocytic activity.[3,12,35] The fractional clearance rate "k" was calculated from the expression:

$$\text{"k" (fractional clearance rate)} = \frac{0.693}{t\frac{1}{2}}$$

where, "k" represents the fraction of the blood volume cleared of the test colloid per minute. Liver sinusoidal blood flow was calculated from the expression:

$$\text{Hepatic blood flow (HBF)} = \text{"k"} \times \text{BV}$$

where BV is the blood volume in ml. calculated by extrapolation of the clearance curve to zero time (Co) and adjusting for dilution of the isotope throughout the vascular compartment.[35] Hepatic blood flow was expressed as ml./min., ml./min./Gm. liver weight, and ml./min./Kg. body weight. Means and standard errors for all experimental groups were calculated and significance was determined with a t-test using a confidence level of 95%. The clearance curve half-time was determined with a PDP digital analog computer (Maynard, Mass.) utilizing a best fit, least squares regression line.

Results

As presented in Table 1, the vascular clearance of the intravenously injected gelatinized "RE test lipid emulsion" was significantly depressed ($p < 0.01$) during the 2, 3, 4 and 5 hr. intervals following the initial abdominal incision. The point of maximum (47%) depression of the phagocytic index K occurred 3 hours following the initial incision, which corresponds with a 2-fold prolongation of the clearance half-time (t½) as compared to control values. The disappearance curve was normal at 1 hr. following the initial incision.

Hepatic sinusoidal blood flow was measured at 1 hour intervals during the experimental period in an attempt to evaluate whether alterations in liver blood flow were a factor in the depression of intravascular phagocytosis. As presented in Table 2, there was no significant change in hepatic sinusoidal blood flow noted either during or following the right hemicolectomy. Furthermore, evaluation of blood volume by extrapolation of the ^{198}Au tracer disappearance curve to zero time and application of the dilution principle, revealed no significant change in blood volume during or following the operative procedure.

In contrast to the apparent lack of involvement of liver blood flow changes in the etiology of the RE phagocytic depression, the findings depicted in Figure 1 demonstrate a close temporal relationship between the level of the phagocytic index K and the circulating plasma opsonic or HRF activity. At 1 hour post-incision there was no alteration in opsonic activity which correlated with a normal phagocytic index (Table 1) at that time. However, the plasma opsonic or HRF activity was significantly ($p < 0.01$) decreased to 75% or less of control preoperative values at 2, 3, and 4 hours following the initial abdominal incision. While the level of HRF activity appears recovered significantly by 5 hrs., the phagocytic index K is still somewhat decreased which may reflect a lag period in terms of the subsequent cellular response.

The apparent involvement of the opsonin system in the etiology of the RE phagocytic depression during operation was supported by the findings presented in Figure 2 in which complete reversal of the surgically induced phagocytic depression was accomplished by prior opsonization of the test colloid. In this regard, prolongation of the half-time (t½) from a control value of 4.88 ± 0.39 min. to 10.08 ± 2.21 min. was circumvented by providing adequate opsonization of the test particles with restoration of a normal clearance (t½ of

TABLE 1. *Intravascular Phagocytic Activity*[(a)] *During and after Operation*

Experimental Parameters[(b)]	Control (Pre-surgery)	Time Following Abdominal Incision (hrs)				
		1	2	3	4	5
Half-Time ($t\frac{1}{2}$) min	4.88 ±0.39	5.86 ±0.48	8.88 ±3.16	10.08 ±2.21	8.28 ±0.52	8.29 ±1.25
Phagocytic Index (K)	.063 ±.004	.051 ±.004	.041 ±.014	.033 ±.006	.036 ±.002	.039 ±.007
K (% Control)	100%	81%	65%	52%	57%	62%

[(a)] Evaluated by the clearance rate of the gelatinized "RE test lipid emulsion" injected intravenously at a dose of 700 mg./Kg. body weight.
[(b)] Each value represents the mean ± standard error with a total of 20 dogs evaluated with approximately 3-4 dogs at each interval.

TABLE 2. *Hepatic Blood Flow(a) and Blood Volume in Dogs Prior to, during and after Right Hemicolectomy*

Experimental Parameter	Control (Pre-surgery)	Time Following Abdominal Incision (hrs)				
		1	2	3	4	5
Hepatic Blood Flow						
ml./min.	539.20 ±3.10	580.10 ±9.80	556.00 ±6.00	545.40 ±42.90	527.10 ±27.30	515.80 ±25.10
ml./min./g.(b)	0.96 ±0.05	1.03 ±0.04	0.94 ±0.06	0.97 ±0.02	0.93 ±0.02	0.91 ±0.05
ml./min./kg.(c)	32.20 ±1.90	34.60 ±1.30	33.30 ±2.10	32.40 ±0.80	31.40 ±0.10	30.60 ±0.10
Blood Volume (ml.)	996 ±2	1001 ±57	1027 ±37	1013 ±2	994 ±6	995 ±3

(a) Collected observations on 12 serial determinations with ^{198}Au injected at a tracer dose of 50 μg./Kg. body weight. Means ± standard error of the mean are presented.

(b) Represents determinations on a per Gm. liver weight basis.

(c) Represents determinations on a per Kg. body weight basis.

5.20 ± 1.50 min.) at 3 hrs. following the initial abdominal incision.

Discussion

The present findings significantly extend previous observations that surgical manipulation of humans[13] and animals[20,33,34,37] will result in an alteration of reticuloendothelial systemic host defense clearance activity. In this regard, a standard right hemicolectomy was performed in dogs during a 3-hour period and a dramatic, two-fold delay in the rate of phagocytic clearance from the vascular space of the foreign test colloid was noted both during and following the operative procedure. The significance of this finding relative to alterations in the general systemic host defense mechanisms[3,18,27,35] is apparent. Since the RES is a major mechanism for the removal of foreign[5] as well as denatured endogenous[18] particulate matter, the potential exists for hematogenous dissemination of malignant cells, bacteria, microthrombi or other blood-borne particulate matter during a time of surgically induced depression in the systemic RE clearance capacity. That impaired clearance by splanchnic RE organs (liver and spleen) could eventuate in an abnormal pulmonary localization of blood-borne particulate matter has been recently demonstrated.[33]

Since a major portion of the cell population of the RES consists of hepatic Kupffer cells, impaired hepatic sinusoidal perfusion would conceivably give rise to an alteration of splanchnic clearance activity. The present findings do not support this vascular mechanism in the etiology of RE depression associated with operation since no alterations in hepatic sinusoidal blood flow were noted any time during or following the operative period, including the interval at which there was maximum phagocytic depression. This observation, coupled with previous findings in rats relative to liver blood flow after laparotomy[37] does not support earlier speculations by Donovan[22] on the potential involvement of liver vascular alterations

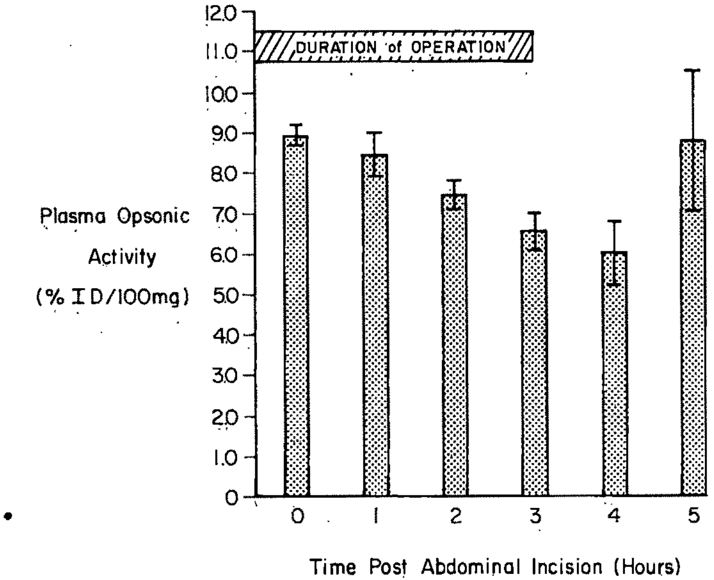


FIG. 1. Circulating plasma opsonic or humoral recognition factor activity during and after operation. Each point represents the mean ± standard error of an average of 44 determinations. Collective data were obtained in 23 separate dogs. Points of opsonic activity deficit (at the 2, 3, and 4 hr. intervals) were significant ($p <$ 0.01).

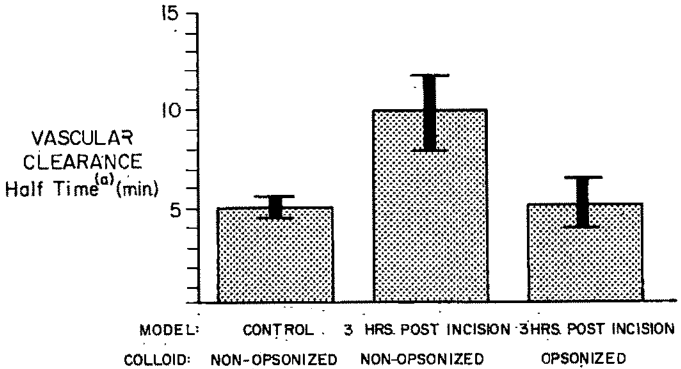


FIG. 2. Recovery of depressed RE phagocytic function during operation by opsonization.

a) Values are expressed as mean ± standard error based on experiments conducted in dogs.

b) The test colloid in the opsonized form and non-opsonized form was injected intravenously at a dose of 700 mg/Kg.

in the abnormal clearance of denatured human serum albumin (HSA) in patients following operation.

In contrast, these results support the concept that RE depression occurring in conjunction with or following surgical stress is related to a decrease in circulating opsonic of HRF activity.[34] Many investigators have clearly demonstrated the intimate role played by serum opsonins[9] in the regulation of phagocytosis.[15,23,30,31,36] Indeed, a negative feedback model has recently been developed which emphasizes the role of humoral factors in the regulation of RE host defense activity as it may relate to macrophage alterations during neoplasia, starvation, RE blockage, x-irradiation, as well as drug induced immunosuppression mediated by failure of the macrophage in the afferent arc of the immune response.[35] Decreased circulating opsonic activity during a period of surgically induced RE phagocytic depression, coupled with the complete reversal of the RE phagocytic depression accomplished by prior opsonization, supports the concept of a "humoral recognition" deficit as a major pathophysiologic factor mediating the depression in intravascular phagocytosis.

The factors mediating depression or depletion of plasma opsonic or HRF activity during or immediately following operative stress are unknown. Effete cellular tissue debris and denatured proteins such as fibrin are rapidly cleared from the circulation by the RES[18,35] and one would strongly suggest that opsonic protein is utilized or consumed in the process.[20,34,35,45] Intracellular debris, microthrombi or other particulate matter may be released into the circulation at the time of operation resulting in the utilization of opsonic protein with subsequent "hypo-opsonemia" and phagocytic depression, a conceptual model analogous to RE blockade.[36] This model appears quite plausible in view of the close *in vivo* similarity between opsonin recovery after operation[33] and after colloid induced opsonin consumption[36] in the rat. Indeed, the similar response of the RES after skin transplantation,[20] laparotomy,[33] trauma,[32] and burn injury[24,27] suggested a common etiologic mechanism.

Activation of the pituitary-adrenal axis with the subsequent release of adrenal cortical steroids in response to tissue trauma is well known. Large doses of steroids have been shown to depress the phagocytic capacity of the RES[21,46] and recent evidence suggests that corticosterone or ACTH, given in amounts to simulate posttrauma levels, may have a depressing effect on the clearance capacity of the RES.[42] Conceivably, adrenal cortical steroids may bind to and transiently inactivate opsonin as previously speculated[37] thus, potentiating and/or precipitating the RE depression associated with surgical trauma. At the present time, the role of adrenal steroid release in the etiology of the RE depression is under investigation and preliminary findings indicate that inhibition of ACTH release by dexamethasone pretreatment eliminates the RE depression during operation (Scovill and Saba, unpublished observations). Whether this is mediated through a cellular or humoral mechanism remains to be determined.

Thus, the findings clearly demonstrate a RE host-defense depression associated with operation which is mediated by a humoral recognition factor (HRF) deficiency. Although the mechanism involved in the depletion of plasma opsonic or HRF activity are not known, the fact that surgical manipulation will induce a major deficit in macrophage function is very significant. Profound phagocytic depression during operation may effect the postoperative response of patients following major operative procedures by interference with non-specific defense mechanisms (bacterial clearance, fibrin clearance, etc.) as well as disruption of the afferent arc of the immune response in terms of antigen localization and processing. Reversal of the RE phagocytic depression by opsonization suggests that circumvention of the RE phagocytic depression and subsequent host defense alterations during operation may be accomplished by the passive administration during operation of opsonically active protein now that it has been isolated, identified, and maintained in a lyophilized form.[1]

Summary

Pronounced depression of the intravascular phagocytic capacity of the reticuloendothelial system was demonstrated in dogs both during and after major abdominal surgery. No alterations in hepatic sinusoidal blood flow or circulating blood volume occurred during the experimental period that could account for the abnormal clearance activity of the RES. In contrast, macrophage depression associated with surgical trauma was functionally related to a depletion and/or inactivation of plasma opsonic or humoral recognition factor (HRF) activity. The RES depression during operation was successfully eliminated by passive opsonin administration in the form of preinjection colloid opsonization. The potential depletion of opsonic protein by the entrance of damaged tissue or denatured protein in the circulation or the consumption of opsonin at the site of tissue injury may trigger this state of "hypo-opsonemia." In addition, preliminary findings suggest a role for the pituitary-adrenal axis in this response. Thus, host defense depression during and after operation due to a "humoral recognition deficiency" would present a precarious balance between resistance and the dissemination of blood-borne, potentially harmful, particulate matter.

References

1. Allen, C., Saba, T. M., Molnar, J.: Isolation and Characteristics of Serum Opsonic Protein Stimulating Phagocytosis and Agglutination of Colloids. Fed. Proc., 31:929, 1971.
2. Benacerraf, B., Biozzi, G. Halpern, B. N. and Stiffel, C.: Physiology of Phagocytosis by the Reticuloendothelial Sys-

tem. *In* Halpern, B. N. (ed) Physiopathology of the Reticuloendothelial System. Blackwell, Oxford. 1957, pp. 52–79.

3. Biozzi, G. and Stiffel, C.: The Physiopathology of the Reticuloendothelial Cells of the Liver and Spleen. *In* Popper, H. and Schaffner, F. (eds) Progress in Liver Diseases. 1965, pp. 166–191.
4. Bohme, D. H.: The Reticuloendothelial System and Nonspecific Resistance. Ann. N.Y. Acad. Sci., 88:172, 1960.
5. Boyden, S.: Cellular Recognition of Foreign Matter. Inter. Rev. Exp. Pathol. 2:311, 1963.
6. Buinaukas, P., McDonald, G. O. and Cole, W. H.: Role of Operative Stress on the Resistance of the Experimental Animal to Innoculated Cancer Cells. Ann. Surg., 148:642, 1958.
7. Cornell, R. P., and Saba, T. M.: Vascular Clearance and Metabolism of Lipid by the Reticuloendothelial System in Dogs. Am. J. Physiol., 221:1511, 1971.
8. Diller, I. C., Mankowski, Z. T. and Fisher, M. E.: The effect of Yeast Polysaccharide on Mouse Tumor. Cancer Res., 23: 201, 1963.
9. DiLuzio, N. R., Pisano, J. C., and Salky, N. K.: Macrophage recognition Mechanisms: Clinical and Experimental Considerations. Adv. Exp. Med. Biol., 15:373, 1971.
10. DiLuzio, N. R. and Riggi, S. T.: The Development of a Lipid Emulsion for the Measurement of Reticuloendothelial Function. J. Reticuloendothel. Soc. 1:136, 1964.
11. Dobson, E. L.: Factors Controlling Phagocytosis. *In* Halpern, B. N. (ed) Physiopathology of the Reticuloendothelial System. Blackwell, Oxford. 1957, pp. 80.
12. Dobson, E. L. and Jones, H. B.: The Behavior of Intravenously Injected Particulate Matter. Acta. Med. Scand. Suppl., 273:1, 1952.
13. Donovan, A. J.: The Effect of Surgery on Reticuloendothelial Function. Arch. Surg., 94:247, 1967.
14. El Rifi, K. Bacon, B., Mehigan, J., Hoppi, E. and Cole, W. H.: Increased Incidence of Pulmonary Metastases after Celiotomy: Counteraction by Heparin. Arch. Surg., 91:625, 1965.
15. Filkins, J. P. and Smith, J. J.: Plasma Factors Influencing Carbon Phagocytosis in the Isolated Perfused Rat Liver. J. Reticuloendothelial Soc., 4:431, 1967.
16. Fisher, B. and Fisher, E. R.: Experimental Studies of Factors Influencing Hepatic Metastases. III. Effect of Surgical Trauma with Special Reference to Liver Injury. Ann. Surg., 150:731, 1959.
17. Fisher, B. and Fisher, E. R.: Host Factors Influencing the Development of Metastases. Surg. Clin. North Am., 42:335, 1962.
18. Gans, H. and Lowman, J.: The Uptake of Fibrin and Fibrin-degradation Products by the Isolated Perfused Rat Liver. Blood, 29:526, 1967.
19. Gordon-Taylor, G.: The Incomputable Factor in Cancer Prognosis. Br. Med. J., 1:455, 1959.
20. Gotjamamos, T.: The Response of the Reticuloendothelial System to Skin Transplantation. Aust. J. Exp. Biol. Med. Sci., 49:259, 1971.
21. Heller, J. H.: Cortisone and Phagocytosis. Endocrinology, 56: 80, 1955.
22. Hershey, S. G. and Altura, B. M.: Function of the Reticuloendothelial System in Experimental Shock and Combined Injury. Anesthesiology, 30:138, 1969.
23. Jenkin, C. R. and Rowley, D.: The Role of Opsonins in the Clearance of Living and Inert Particles by Cells of the Reticuloendothelial System. J. Exptl. Med., 114:365, 1961.
24. Lemperle, G.: Reticuloendothelial System in the Burned Rat. J. Infect. Dis., 117:7, 1967.
25. Lewis, M. R. and Cole, W. H. Experimental Increase of Lung Metastases after Operative Trauma. Arch. Surg., 77:621, 1958.
26. Miles, A. A.: Local Defenses Against Infection and their Relation to the General Reticuloendothelial Defenses. *In* Halpern, B. N. (ed) Physiopathology of the reticuloendothelial system. Blackwell, Oxford, 1957, pp. 108.
27. Munster, A. M.: Alterations of the Host Defense Mechanism in Burns. Surg. Clin. North Am., 50:1217, 1970.
28. Old, L. J., Benacerraf, B., Clarke, D. A., Carswell, E. A. and Stockert, E.: The Role of the Reticuloendothelial System in the Host Reaction to Neoplasia. Cancer Res., 21:1281, 1961.
29. Old L. J., Clarke, D. A., and Benacerraf, B.: Effect of *Bacillus Calmette-Guerin* (BCG) Infection on Transplanted Tumors in the Mouse. Nature, 184:291, 1959.
30. Pisano, J. C., DiLuzio, N. R. and Salky, N. K.: Absence of Macrophage Humoral Recognition Factor(s) in Patients with Carcinoma. J. Lab. Clin. Med., 76:141, 1970.
31. Pisano, J. C., Filkins, J. P. and DiLuzio, N. R.: Development and Evaluation of a Method for the Isolation of Kupffer Cells. J. Reticuloendothel. Soc., 4:431, 1967.
32. Rittenbury, M. S. and Hanback, L. D.: Phagocytic Depression in Thermal Injuries. J. Trauma, 7:523, 1967.
33. Saba, T. M.: Effect of Surgical Trauma on the Clearance and Localization of Blood-borne Particulate Matter. Surgery (in press), 1972.
34. Saba, T. M.: Mechanism Mediating Reticuloendothelial Depression after Surgery. Proc. Soc. Exp. Biol. Med., 133:1132, 1970.
35. Saba, T. M.: Physiology and Physiopathology of the Reticuloendothelial System (Review Article) Arch. Intern. Med., 126:1031, 1970.
36. Saba, T. M. and DiLuzio, N. R.: Reticuloendothelial Blockade and Recovery as a Function of Opsonic Activity. Am. J. Physiol., 216:197, 1969.
37. Saba, T. M. and DiLuzio, N. R.: Surgical Stress and Reticuloendothelial Function. Surgery 65:807, 1969.
38. Saba, T. M., Filkins, J. P. and DiLuzio, N. R.: Properties of the "Opsonic System" Regulating *in vitro* Hepatic Phagocytosis. J. Reticuloendothel. Soc., 3:389, 1966.
39. Salky, N. K., DiLuzio, N. R., Levin, A. G. and Goldsmith, A. S.: Phagocytic Activity of the Reticuloendothelial System in Neoplastic Disease. J. Lab. Clin. Med., 70:393, 1967.
40. Salky, N. K., DiLuzio, N. R., P'Pool, D. B. and Southerland, A. J.: Evaluation of Reticuloendothelial Function in Man. JAMA, 187:744, 1964.
41. Salky, N. K., Miles, D., DiLuzio, N. R.: Activity of the reticuloendothelial System in Diseases of Altered Immunity. J. Lab. Clin. Med., 70:393, 1967.
42. Schildt, B. B. and Löw, H.: Relationship Between Trauma, Plasma Corticosterone and Reticuloendothelial Function in Anesthetized Mice. *Acta Endocrinol.*, 67:141, 1971.
43. Southam, C. M.: Are There Host Defenses Against Cancer? M. Clin. North Am., 45:733, 1961.
44. Subramanian, V., Lowman, J. R. and Gans, H.: Effect of Extracorporeal Circulation on Reticuloendothelial Function. Arch. Surg., 97:330, 1968.
45. Vaughn, R. G.: The Discriminative Behavior of Rabbit Phagocytosis. Br. J. Exp. Pathol., 46:71, 1964.
46. Wiener, J., Cottrell, T. S., Margaretten, W. and Spiro, D.: An Electronmicroscopic Study of Steroid Induced Reticuloendothelial Blockade. Am. J. Pathol., 50:187, 1967.

Clinical Comparison of the End-to-Side and Side-to-Side Portacaval Shunt:

Ten Year Follow-up

SHUNZABURO IWATSUKI, M.D.,* WILLIAM P. MIKKELSEN, M.D.,
ALLAN G. REDEKER, M.D., TELFER B. REYNOLDS, M.D., FRED L. TURRILL, M.D.

From the Departments of Medicine and Surgery, University of Southern California School of Medicine and the Los Angeles County—University of Southern California Medical Center, Los Angeles, California 90033

BETWEEN 1959 AND 1962, end-to-side (ES) or side-to-side (SS) portacaval shunt was performed in two groups of 40 patients each on the University of Southern California surgical service at the Los Angeles County General Hospital. Preliminary results, to June 1965, were reported in 1966.[16] At that time the results of the two operations seemed similar except for a three times greater incidence of severe hepatic encephalopathy after SS shunt.

The advisability of portacaval shunting is being increasingly questioned because of disability from postoperative hepatic encephalopathy. In addition, there is still disagreement as to which type of shunt is preferable. Therefore, it was thought worthwhile to review and present the course of our patients for an additional six years, to June 1971.

Clinical Material

The details of patient selection, surgical procedure, time under anesthesia, blood replacement requirement and postoperative course are listed in our earlier publication. In brief, the choice of shunt was not statistically randomized but rather was based on anatomic considerations at operation. The two groups of 40 patients were comparable with regard to type of disease, age, sex, preoperative liver function, duration of operation and average blood replacement. Thirty-eight patients in each group had alcoholic liver disease.

Patients Lost to Follow-up Study

As of June 1965, contact had been lost with nine patients in the ES and five in the SS group. Since then we have been able to follow nearly all of the patients and have reestablished contact with some of those previously lost so that follow-up data are incomplete in only nine patients. Four were lost in the first 2 years, three in the fourth, one in the eighth and one in the tenth year.

Deaths Since Operation

Eighteen patients from each group were known to be dead in June 1965. As of June 1971, there have been 29 known deaths of ES patients and 30 among those with SS shunt. Survival is depicted in Figure 1 and in Table 1 using the life table method as described by Cutler and Ederer.[4] The cause and timing of deaths are shown in Table 2. Hepatic failure has been the major cause of death with essentially the same frequency in both groups. Seven ES and five SS patients are known to be alive and all are in reasonably good health except for one SS shunt patient with mild recurring

---

Submitted for publication March 22, 1972.

Supported in part by a research grant (HE 01718) from the National Institutes of Health.

No reprints available.

* Present address: Department of Surgery, University of Colorado Medical Center, Denver, Colorado.

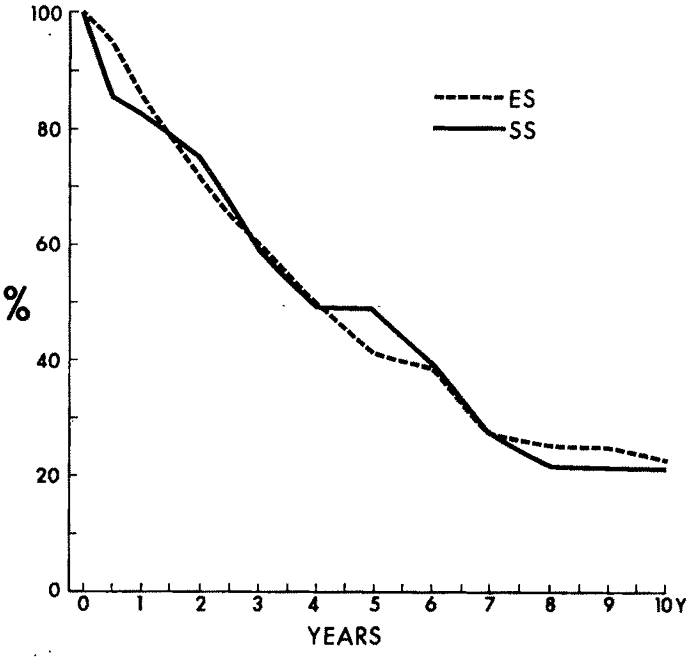


FIG. 1. Cumulative survival (life-table method) after ES and SS portacaval shunt.

encephalopathy. All but one of these 12 patients deny resumption of alcohol intake and we have no reason to doubt them. The twelfth patient has just recently returned to intermittent drinking, 9 years after the shunt operation. A total of 21 ES and 19 SS patients are known to have returned to heavy drinking at some point after operation, often a number of years afterward.

Gastrointestinal Bleeding

There have been eight known episodes of gastrointestinal bleeding since operation in the patients with ES shunt and ten in the patients with SS shunt. Bleeding was judged to be the major factor contributing to death of nine patients (Table 2). Since the previous report, one ES patient had fatal bleeding 78 months after operation with no recognizable source at autopsy other than persistent esophageal varices. Bleeding from a duodenal ulcer contributed to death from hepatic failure in another patient 7 years postoperatively. We recently discovered that a third patient died at another hospital 38 months after operation with massive bleeding and no identifiable source at autopsy other than esophageal varices. All three patients had patent shunts.

One additional bleeding episode has occurred in the group of patients with SS shunt. In this patient, moderate bleeding developed during protracted hepatic coma 72 months postoperatively. Small gastric erosions were found at autopsy; the shunt was open.

Postoperative Encephalopathy

The method of classification of postoperative hepatic encephalopathy is described in detail in our previous

TABLE 1. *Survival after ES and SS Portacaval Shunt Using the Life-Table Method*[4]

Years after E-S shunt	Alive at Beginning of Interval	Died during Interval	Lost to Follow-up during Interval	Withdrawn Alive during Interval	Effective NumberExposed to Risk of Dying	Cumulative Proportion Surviving from Shunt Thru End of Interval	Standard Error of Survival Rate
0–1	40	6	2	—	39	0.846	0.058
1–2	32	5	1	—	31.5	0.712	0.073
2–3	26	4	—	—	26	0.602	0.080
3–4	22	4	—	—	22	0.493	0.082
4–5	18	3	—	—	18	0.411	0.081
5–6	15	1	—	—	15	0.383	0.080
6–7	14	4	—	—	14	0.274	0.074
7–8	10	1	—	—	10	0.246	0.071
8–9	9	—	—	—	9	0.246	0.071
9–10	9	1	1	—	8.5	0.217	0.068
10–11	7	—	—	4	5	0.217	0.068
Years after S-S shunt							
0–1	40	7	—	—	40	0.825	0.060
1–2	33	3	1	—	32.5	0.749	0.069
2–3	29	6	—	—	29	0.594	0.078
3–4	23	4	3	—	21.5	0.483	0.081
4–5	16	—	—	—	16	0.483	0.081
5–6	16	3	—	—	16	0.393	0.081
6–7	13	4	—	—	13	0.272	0.075
7–8	9	2	1	—	8.5	0.208	0.070
8–9	6	—	—	—	6	0.208	0.070
9–10	6	—	—	2	5	0.208	0.070
10–11	4	1	—	1	3.5	0.149	0.071

TABLE 2. *Causes and Timing of Deaths after ES and SS Portacaval Shunt*

	Postoperative Years											
Causes of Death	1*	2	3	4	5	6	7	8	9	10	11	Total
ES Group												
Hepatic failure	4	3	2	2	2	—	1	—	—	—		14
GI bleeding												
ulcer	1	1					1					3
varices	1			1			1					3
Unrelated disease		1	2		1		1	1		1		7
Uncertain				1		1						2
SS Group												
Hepatic failure	5	2	4	2		2	2	1			1	19
GI bleeding												
ulcer			1									1
varices	2											2
Unrelated disease		1		2			2					5
Uncertain			1			1		1				3

* includes 8 "operative" deaths occurring within 2 months of operation.

publication. Severe encephalopathy is defined as repeated episodes of confusion or coma sufficient to interfere with the patient's activities or to require hospitalization. Since 1965, two additional patients in each group have manifested encephalopathy and in one patient in each group it has been severe. The ages of the latter two patients were 59 and 63 years at the time of operation. Of 37 patients with ES shunt followed six months or more, four (11%) developed severe encephalopathy as compared to ten of 33 SS shunt patients (30%). All 14 of the patients with severe encephalopathy have died, in most instances from hepatic failure. Figure 2 shows the timing of onset of severe encephalopathy, the age at operation and the duration of life. Patients continued to develop this complication for the first time as late as 5 years postoperatively.

Miscellaneous Features

Since our first report, none of the patients have developed ascites or clinical hypersplenism. Hepatic function tests have generally remained stable in patients who did not return to alcoholism or develop concurrent disease.

Discussion

Random allocation of our patients to SS or ES shunt would have been preferable from a statistical standpoint but was deemed impractical because of difficulty in constructing SS shunt in patients whose portal vein and inferior vena cava were not close together. Though the allocation was not random, there was no apparent difference between the two groups preoperatively with regard to the usual parameters of age, sex, type of disease and hepatic function test results.

Since our previous article, there have been several publications comparing ES and SS shunt. Zuidema and Kirsh compared results in 31 patients receiving ES shunt and 42 receiving SS shunt.[22] The choice of shunt was based on anatomic factors. Surgical mortality was 19% in each group. The incidence of postshunt encephalopathy was 30% after SS shunt and 13% after ES shunt. Turcotte, Wallin and Child have summarized their portacaval shunt experience between 1959 and 1967 which included 58 ES and 44 SS operations.[18] Choice of shunt was based on several factors and there was no attempt to accumulate comparable groups of patients. They concluded that there was little overall difference in the results of the two operations except that operative mortality seemed less with SS shunt than with ES shunt in "poor risk" patients. There was a 27% incidence of severe recurrent encephalopathy in SS shunt survivors compared to a 12.5% incidence after ES shunt. Panke, Rousselot and Burchell have described their extensive experience with both types of shunt in two publications.[2,11] In 210 ES shunts, usually performed because of variceal hemorrhage, postoperative encephalopathy was noted in 26% but was severe in only 8%. In 63 SS shunts, usually performed for refractory ascites, there was a 16% incidence of severe encephalopathy. The 5-year sur-

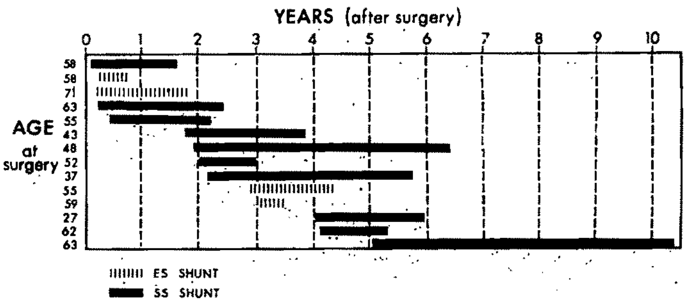


FIG. 2. Timing of onset of severe hepatic encephalopathy and duration of life in 14 patients after ES and SS portacaval shunt.

vival curve was impressively better for those with SS shunt but the authors pointed out that the number of these patients followed for 5 years was still quite small at the time of the publication. Britton, Voorhees and Price reported a slightly higher incidence of encephalopathy after ES than SS shunt in a group of 324 patients, three-quarters of whom had ES shunt.[19] They pointed out that a longer period of follow-up in the ES patients might account for the greater incidence of encephalopathy since the complication was more frequent in patients followed for more than 5 years. Orloff also found a slightly greater frequency of encephalopathy in 25 patients having emergency ES shunt as compared to 15 patients receiving emergency SS shunt.[10]

Our two groups of SS and ES shunt patients seem more comparable at the time of operation than do those in the other reports cited above, with the probable exception of the patients of Zuidema and Kirsh.[22] Our findings are similar at 5-year and 10-year follow-up and show a substantially higher incidence of encephalopathy after SS shunt (33% vs. 11%). Using the chi square method of statistical comparison, there is a 5–10% possibility that this observed difference could have occurred by chance ($p < 0.10, > 0.05$). Patients continued to develop the first manifestations of severe encephalopathy as long as 5 years after the shunt.

It is surprising that survival in our ES and SS shunt patients is nearly identical after 10 years since the greater incidence of recurring encephalopathy might be expected to increase mortality in the SS group. Overall, slightly less than half of our patients were alive 5 years and one-fifth were alive 10 years after operation. Five year survivals in other large shunt series vary from 20 to 58%, probably reflecting differences in selection criteria for surgery.[2;7,11,18,19,20] No mortality figures are available for entirely comparable patients not undergoing shunt operation. Five year survival of patients with esophageal varices who were followed as control subjects in studies of prophylactic portacaval shunt were 51%,[15] 64%[3] and 64%.[6] Tables constructed by Ratnoff and Patek,[13] Garceau and colleagues[5] and Powell and Klatskin[12] for patients with alcoholic liver disease show values ranging all the way from 5.5% to 89% for 5-year survival, depending on the number of complications present at the time of entry into the studies and whether or not alcohol ingestion ceased.

The reason for the apparently greater incidence of encephalopathy after SS shunt is conjectural. Portal flow is entirely into the vena cava in most patients after SS shunt[1,9] as it is after ES shunt. Hepatic venous flow is reduced more after SS shunt because of backflow of hepatic arterial blood through the hepatic limb of the portal vein to the vena cava.[8,14,17,21] Possibly this favors encephalopathy by reducing total hepatic clearance of whatever compound or compounds are responsible for the central nervous system effects.

Summary

Two groups of 40 patients received end-to-side (ES) or side-to-side (SS) portacaval shunt for the treatment of portal hypertension between 1959 and 1962 and have been followed since that time. The choice of shunt was based on anatomic factors found at operation. The groups were comparable in regard to age, sex, type of disease, preoperative liver function and duration of operation.

Survival has been essentially equal in the two groups, with nearly 50% of the patients alive 5 years and 20% alive 10 years postoperatively. Severe hepatic encephalopathy developed in ten patients with SS and four with ES shunt. Encephalopathy appeared for the first time as long as 5 years after operation. All 14 patients with severe encephalopathy have expired. In all other respects, the results of the two types of shunts seem similar.

References

1. Britton, R. C., Voorhees, A. B., Jr. and Price, J. B., Jr.: Perfusion of the Liver Following Side-to-side Portacaval Shunt. Surgery, 62:181, 1967.
2. Burchell, A. R., Rousselot, L. M. and Panke, W. F.: A Seven Year Experience with Side-to-side Portacaval Shunt for Cirrhotic Ascites. Ann. Surg., 168:655, 1968.
3. Conn, H. O. and Lindenmuth, W. W.: Prophylactic Portacaval Anastomosis in patients with Esophageal Varices. N. Engl. J. Med., 279:725, 1968.
4. Cutler, S. J. and Ederer, F.: Maximum Utilization of the Life Table Method in Analyzing Survival. J. Chronic Dis., 8:699, 1958.
5. Garceau, A. J., Chalmers, T. C. and the Boston Inter-Hospital Liver Group: The natural history of cirrhosis. I Survival with esophageal varices. N. Engl. J. Med., 268:469, 1963.
6. Jackson, F. C., Perrin, E. B., Smith, A. G., Dagradi, A. E. and Nadal, H. M.: A Clinical Investigation of the Portacaval Shunt. II Survival Analysis of the Prophylactic Operation. Amer. J. Surg., 115:22, 1968.
7. McDermott, W. V., Jr., Palazzi, H., Nardi, G. L. and Mondet, A.: Elective Portal Systemic Shunt: Analysis of 237 Cases. N. Engl. J. Med., 264:419, 1961.
8. Moreno, A. H., Burchell, A. R., Rousselot, L. M., Panke, W. F., Slafsky, S. F. and Burke, J. H.: Portal Blood Flow in Cirrhosis of the Liver. J. Clin. Invest., 46:436, 1967.
9. Mulder, D. G., Plested, W. G., III, Hanafee, W. N. and Murray, J. F.: Hepatic Circulatory and Functional Alterations Following Side-to-side Portacaval Shunt. Surgery, 59:923, 1966.
10. Orloff, M. J.: Emergency Portacaval Shunt: A Comparative Study of Shunt, Varix Ligation and Nonsurgical Treatment of Bleeding Esophageal Varices in Unselected Patients with Cirrhosis. Ann. Surg., 166:456, 1967.
11. Panke, W. F., Rousselot, L. M. and Burchell, A. R.: A Sixteen-year Experience with End-to-side Portacaval Shunt for Variceal Hemorrhage. Ann. Surg., 168:957, 1968.

12. Powell, W. J., Jr. and Klatskin, G.: Duration of Survival in Patients with Laennec's Cirrhosis. Am. J. Med., **44**:406, 1968.
13. Ratnoff, O. D. and Patek, A. J., Jr.: The Natural History of Laennec's Cirrhosis of the Liver. Medicine, **21**:207, 1942.
14. Redeker, A. G., Kunelis, C. T., Yamamoto, S. and Reynolds, T. B.: Assessment of Portal and Hepatic Hemodynamics After Side-to-side Portacaval Shunt in Patients with Cirrhosis. J. Clin. Invest., **43**:1464, 1964.
15. Resnick, R. H., Chalmers, T. C., Ishihara, A. M., Garceau, A. J., Callow, A. D., Schimmel, E. T., O'Hara, E. T. and the Boston Inter-Hospital Liver Group: A Controlled study of the Prophylactic Portacaval Shunt. Ann. Int. Med., **70**:675, 1969.
16. Reynolds, T. B., Hudson, N. M., Mikkelsen, W. P., Turrill, F. L. and Redeker, A. G.: Clinical Comparison of End-to-side and Side-to-side Portacaval Shunt. N. Engl. J. Med., **274**:706, 1966.
17. Reynolds, T. B., Mikkelsen, W. P., Redeker, A. G. and Yamahiro, H. S.: Effect of Side-to-side Portacaval Shunt on Hepatic Hemodynamics in Cirrhosis. J. Clin. Invest., **41**:1242, 1962.
18. Turcotte, J. G., Wallin, V. W., Jr. and Child, C. G., III: End-to-side Versus Side-to-side Portacaval Shunts in Patients with Hepatic Cirrhosis. Amer. J. Surg., **117**:108, 1969.
19. Voorhees, A. B., Price, J. B., Jr. and Britton, R. C.: Portasystemic Shunting Procedures for Portal Hypertension. Am. J. Surg., **119**:501, 1970.
20. Wantz, G. E. and Payne, M. A.: Experience with Portacaval Shunt for Portal Hypertension. N. Engl. J. Med., **265**:721, 1961.
21. Warren, W. D. and Muller, W. H.: A Clarification of Some Hemodynamic Changes in Cirrhosis and Their Surgical Significance. Ann. Surg., **150**:413, 1959.
22. Zuidema, G. D. and Kirsh, M. M.: Hepatic Encephalopathy Following Portal Decompression: Evaluation of End-to-side and Side-to-side Anastomosis. Am. Surgeon, **31**:567, 1965.

Selection of Patients with Portal Hypertension for Splenorenal Shunt

DAVID P. CAMPBELL, M.D., CONSTANTINE E. ANAGNOSTOPOULOS, M.D.
AND WILLIAM W. L. GLENN, M.D.

From the Department of Surgery, Yale University School of Medicine New Haven, Connecticut

THERE IS STILL controversy in the literature concerning the type of portal-systemic shunt to perform in patients with portal hypertension complicated by bleeding from esophageal varices.[3,9,11,16] Many reports show satisfactory results after portacaval shunting, but a small number of surgeons claim better results after splenorenal shunting.[8,9,12] It is obvious that splenectomy and splenorenal anastomosis is indicated where there is an extrahepatic portal obstruction, but other indications for this procedure, which is usually more difficult to perform than portacaval anastomosis, have not been well defined.

Seventy-six portal-systemic shunts were performed at Yale-New Haven Hospital between 1952 and 1965. An end-to-side portal vein to inferior vena cava shunt was made in most patients to decompress the portal system, but in approximately one quarter of the total series a splenorenal shunt was established. It is the purpose of this paper to review these shunts, all performed more than 5 years ago, with specific reference to the indications for splenectomy and splenorenal anastomosis. The patients who underwent splenorenal shunts will also be compared with those patients who underwent portacaval anastomoses.

Method

All portal systemic shunts performed at the Yale-New Haven Hospital before 1965 were reviewed. This time interval was chosen to provide at least a 5-year follow-up period on all patients. All shunts were performed because of portal hypertension complicated by bleeding from esophageal varices. Most were performed after control of the bleeding episode and stabilization of the patient. Preoperative splenoportograms were done on nearly all the patients. Follow-up data were obtained via the hospital clinics and, when necessary, through telephone or postal contact with the patient or his physician.

Evaluation of the post-shunt patients included: 1) period of survival; 2) presence or absence of variceal bleeding; 3) presence or absence of ammonia intoxication; and 4) quality of survival. Ammonia intoxication is defined as an abnormality of cerebral function associated with an elevated blood ammonia concentration. Excellent quality of survival is defined as survival with normal activity and without evidence of ammonia intoxication or upper gastrointestinal bleeding.

Results

In the period 1952–1965, 76 shunts were performed, of which 22 were splenorenal. Five-year follow-up data are available on all the splenorenal shunts. Three patients with portacaval shunts, however, have been lost to follow-up (Table 1).

Patients with splenorenal shunts were divided into five groups according to the indication for the shunt (Table 2).

Group I. Extrahepatic Portal Obstruction

Splenectomy and a splenorenal shunt were performed in two children, ages 6 and 7, with extrahepatic portal

---

Submitted for publication June 23, 1972.

Preliminary report presented at the Halsted Society Meeting Nashville, Tennessee 1969.

Reprint requests: Dr. David P. Campbell, Division of Pediatric Surgery, University of Oklahoma Medical Center, 800 N.E. 13th Street, Oklahoma City, Oklahoma 73190.

vein obstruction. Both patients are still alive, 7 and 15 years later, with excellent quality of survival (Table 3).

Group II. Intrahepatic Portal Obstruction with Hypersplenism

Seven patients with cirrhosis, portal hypertension and severe hypersplenism underwent a splenorenal shunt. Severe hypersplenism was arbitrarily defined as a white blood cell count below 3,000 mm^3. and a platelet count below 50,000 mm^3. There was no operative mortality in this group. Five patients survived 5 years, three having an excellent quality of survival. Post-shunt ammonia intoxication developed in two patients and in the same number there was a recurrence of bleeding from the varices. One patient died 2 years after operation from complications of a perforated duodenal ulcer. A second patient died 2 years after operation from upper gastrointestinal bleeding of undetermined etiology. Five-year follow-up of the five survivors shows all with normal white blood cell and platelet counts.

Group III. Intrahepatic Portal Obstruction with Technical Problems Preventing Portacaval Shunt

Splenorenal shunts were performed in six patients for whom previously planned portacaval shunts could not be performed for various technical reasons. The problems encountered included acute cholecystitis, adhesions secondary to previous biliary tract surgery, varix of the portal vein and adhesions secondary to previous gastroduodenal surgery. There was one operative death. Post-shunt ammonia intoxication occurred in three patients and there was a recurrence of bleeding in one patient. Four patients survived 5 years, two having an excellent quality of survival.

TABLE 1. *Portasystemic Shunts Yale-New Haven Hospital 1952–1965*

Type of Shunt	Number	Follow-up Data Available
Splenorenal	22	22 (100%)
Portacaval	54	51 (94.5%)
Total:	76	73 (96%)

TABLE 2. *Indications for Splenorenal Shunt*

Group I.	Extrahepatic portal obstruction
Group II.	Intrahepatic portal obstruction with hypersplenism
Group III.	Intrahepatic portal obstruction with technical problems preventing portacaval shunt
Group IV.	Combined intra- and extrahepatic portal obstruction
Group V.	Portal hypertension with no demonstable obstruction

Group IV. Combined Intrahepatic and Extrahepatic Portal Obstruction

Five patients with cirrhosis underwent splenorenal shunts after a thrombosed portal vein was found at operation or on preoperative splenoportography. There was one operative death. The shunt in this case was clotted at post-mortem examination. Two patients survived 5 years. Three patients experienced post-shunt ammonia intoxication and two bled again from varices. One patient died 4 years after operation with a bleeding duodenal ulcer. A second patient died 21 months after operation from gastrointestinal bleeding, secondary to both varices and a duodenal ulcer. In only one patient was there an excellent quality of survival.

Group V. Portal Hypertension with No Demonstrable Obstruction

Two patients, 10 and 22 years of age, bled from esophageal varices but had no demonstrable mechanical block on either splenoportography or liver biopsy. A splenectomy and splenorenal anastomosis were performed on the assumption that portal hypertension was secondary to increased portal flow, possibly on the basis of abnormal A-V shunting. One patient, a 10-year-old girl, had a repeat liver biopsy 4 years postoperatively which demonstrated a normal lobular pattern in all areas but considerable sinusoidal congestion and distention in the midzonal areas of about one-half the lobules. She is now 15 years postoperative. She has had three normal deliveries and has not bled again from the varices nor had any evidence of ammonia intoxication.

TABLE 3. *Results of Portasystemic Shunts*

Shunt	Cases *Number*	Operative Mortality	NH_3 Intoxic.	Variceal Bleeding *Per cent*	5-year Survival	Excellent Quality of Survival
Splenorenal						
Group I	2	0	0	0	100	100
Group II	7	0	28.5	28.5	71.4	42.8
Group III	6	16.7	50	16.7	66.7	33.3
Group IV	5	20	60	40	40	20
Group V	2	0	0	50	100	100
Portacaval	51	22*	51	16	39	22

* Based on 54 cases (three cases lost to follow-up).

TABLE 4. *Portal Pressure Decrease after Shunt Procedure*

Shunt	0–50 mm. H_2O (%)	50–100 mm. H_2O (%)	More than 100 mm. H_2O (%)	Not Recorded (%)
Splenorenal	30	25	33	12
Portacaval	10	19	42	29

The second patient, a 22-year-old man, required transesophageal ligation of the varices prior to splenectomy and splenorenal anastomosis as it was impossible to control the bleeding with a Sengstaken-Blakemore tube. Following creation of the shunt he did well for 5 years, but then rebled on several occasions and died 10 years after shunt operation. Post-mortem examination revealed a partially obstructing septum in the extrahepatic portion of the portal vein as well as partial thrombotic obstruction of many of the intrahepatic branches.

Portacaval Shunts

Fifty-four patients with intrahepatic portal obstruction underwent portacaval shunts at Yale-New Haven Hospital from 1952 to 1965. Fifty of this group had end-to-side shunts and four had side-to-side shunts. The operative mortality was 22%. Postoperative ammonia intoxication occurred in 51% of the patients and actual hepatic coma in 20%. Sixteen per cent of the patients rebled from esophageal varices. Thirty-seven per cent of the total group (half of those who died) died from hepatic failure.

Portal Pressure Studies

Pre- and postoperative portal pressure studies were obtained on 86.4% of the splenorenal shunts and 70% of the portacaval shunts. The recorded decreases in portal pressure were greatest in the portacaval shunts (Table 4).

Discussion

If one compares the five categories of patients who underwent splenorenal shunts with the portacaval group (Table 3), it is obvious that more satisfactory results were obtained in all of the splenorenal categories except Group IV (combined intrahepatic and extrahepatic portal obstruction).

To further study the relative effectiveness of the two types of shunts, the combined splenorenal group was compared with the 54 portacaval shunts (Table 5). The two patients with extrahepatic obstruction (Group I) and the two patients without evidence of intra- or extrahepatic obstruction (Group V) have been excluded from the comparative analysis as they exhibited no intrinsic hepatic disease—a major factor in postoperative morbidity and mortality. The splenorenal groups II, III, and IV thus total 18 shunts.

The splenorenal shunt proved to be superior to the portacaval shunt as regards:

1) operative mortality (11% vs. 22%)
2) 5-year survival (61.1% vs. 39%)
3) excellent quality of survival at 5 years (33.3% vs. 22%)
4) postoperative ammonia intoxication (44.4% vs. 51%)
5) postoperative hepatic coma (5.5% vs. 20%)

The splenorenal shunt was less effective than the portacaval shunt in reducing portal pressure (Table 4) and this was reflected in a higher incidence of postoperative variceal bleeding (27.8% vs. 16%). This has also been the experience of others, although Linton[12] and Hollenbeck[8] found no difference between the two shunts. Thrombosis of the splenorenal shunts undoubtedly contributed to their higher incidence of postshunt variceal bleeding. Autopsies were performed on six of the nine patients who died in the splenorenal group. Two of the six shunts were thrombosed.

Infants with portal vein thrombosis are best treated with a conservative non-operative approach.[1] A mesocaval shunt has been recommended in the older child because of the supposed high incidence of rebleeding after splenorenal shunting.[1,21] We have applied the splenorenal shunt in two children with no rebleeding over a period of many years. Therefore, if the splenic vein is 1 cm. or larger in diameter at the point of intended anastomosis, we recommend a splenorenal shunt rather than risk the complications which might follow ligation of the inferior vena cava as required with the mesocaval shunt.

Patients with severe hypersplenism complicating portal hypertension show, we believe, a clear indication for splenectomy and splenorenal anastomosis. Although in many instances hypersplenism will disappear following adequate decompression of the spleen via a

TABLE 5. *Results of Portasystemic Shunts in Patients With Cirrhosis*

Shunt	Cases *Number*	Operative Mortality	NH_3 Intoxication	Hepatic coma *Per cent*	Variceal Bleeding	5-year Survival	Excellent Quality of Survival
SR	18	11	44.4	5.5	27.8	61.1	33.3
PC	51	22	51	20	16	39	22

portacaval shunt, in some cases the hypersplenism persists,[7,10] or even worsens[17] and requires subsequent splenectomy. In anticipation of persistent hypersplenism, Mulder[15] performs a splenectomy in conjunction with the creation of a portacaval shunt in patients with severe hypersplenism. This seems to be more complicated than splenectomy and splenorenal anastomosis.

In the patient with cirrhosis who develops a thrombosis of the portal vein, splenectomy and splenorenal anastomosis is the procedure of choice. A portacaval shunt after removal of the thrombus from the portal vein, has, in our experience, been followed by prompt recurrence of the thrombotic occlusion.

Splenectomy and splenorenal shunting is also recommended for that group of patients without demonstrable portal block. Some years ago we encountered four such patients.[20] At that time we believed the portal hypertension and variceal bleeding were secondary to increased portal flow as both the splenoportogram and liver biopsy studies in these patients were normal. Subsequent autopsies on two of these patients have demonstrated an intrahepatic block of the portal vein tributaries. This condition, now called hepatoportal sclerosis[14] is due to thickening and sclerosis of the portal vein branches within the liver.

Thrombi in various stages of organization are often found in the veins. Decompression of the portal vein by an end-to-side portacaval anastomosis will, by cutting off the intrahepatic flow entirely, encourage the development or extension of thrombi in the intrahepatic portion of the portal vein.

On the basis of our long-term follow up data, one might argue for the routine use of the splenorenal shunt in patients with portal hypertension as recommended by Linton.[11] We have, in the past, been discouraged from this by the technical difficulties encountered with removal of a large and highly vascular spleen and the uncertainty, even with a preoperative splenoportogram, of finding a splenic vein suitable for anastomosis. The higher incidence of post-shunt variceal bleeding, as demonstrated in our series, has also been used as an argument against the splenorenal shunt. The most significant statistics to be considered, however, are those related to operative mortality, 5-year survival and quality of survival.

Although our splenorenal group is a highly selected one, and not strictly comparable to the portacaval group, the results as regards operative mortality, 5-year survival and quality of survival are obviously superior. One must conclude that: 1) the splenorenal shunt provides very acceptable results in the selective classifications discussed above and 2) the splenorenal shunt appears to be a generally more satisfactory procedure than the portacaval shunt in the patient with portal hypertension complicated by bleeding esophageal varices. Before recommending the splenorenal shunt for routine use in patients with cirrhosis in preference to the portacaval shunt, a randomized prospective comparison should be carried out.

Summary

In the time interval 1952–1965, 76 portal-systemic shunts were performed at Yale-New Haven Hospital for portal hypertension complicated by bleeding esophageal varices. Twenty-two patients had splenectomy and splenorenal anastomoses and 54 had portacaval anastomoses performed. The indications for performing a splenorenal shunt were extrahepatic obstruction, severe hypersplenism, technical problems preventing portacaval anastomosis, combined intra and extrahepatic portal obstruction and portal hypertension without demonstrable obstruction.

Five-year follow-up data of the patients with cirrhosis who had splenorenal shunts performed were compared with those of patients with cirrhosis who had portacaval shunts performed. In terms of operative mortality, postoperative ammonia intoxication, 5-year survival and quality of survival, the results in the patients with splenorenal shunts were superior to those in patients with portacaval shunts.

On the basis of these results and in view of other considerations concerning the preservation of intrahepatic bloodflow, we believe the splenorenal shunt is the procedure of choice in the above groups of patients when a suitable splenic vein is available for splenorenal anastomosis.

Although all of our patients who have undergone splenorenal and portacaval shunts are not comparable, the superior results obtained with the splenorenal shunt suggests that it may be the procedure of choice in most patients requiring portal-systemic shunting.

References

1. Clatworthy, H. W., Jr. and Boles, E. T., Jr.: Extrahepatic Portal Bed Block in Children. Ann. Surg., **150**:371, 1959.
2. Conn, H. O. and Lindenmuth, W. W.: Prophylactic Portacaval Anastomosis in Cirrhotic Patients with Esophageal Varices. N. Engl. J. M., **279**:725, 1968.
3. Crane, C.: The Choice of Shunt Procedure For Cirrhotic Patients with Variceal Bleeding, Ascites, and Hypersplenism. Surg. Gynecol. Obstet., **115**:12, 1962.
4. Fonkalsrud, E. W. and Longmire, W. P., Jr.: Reassessment of Operative Procedures for Portal Hypertension in Infants and Children. Am. J. Surg., **118**:148, 1969.
5. Foster, J. H. and Vetto, R. M.: Fifteen Years' Experience with Porta-systemic Shunting Operations. Am. J. Surg., **33**:514, 1967.
6. Foster, J. H., Holcomb, G. W. and Kirtley, J. A.: Results of Surgical Treatment of Portal Hypertension in Children. Ann. Surg., **157**:868, 1963.

7. Gerwig, W. H., Jr., Countryman, L. K., Harrison, I. and Keshishian, J. M.: Persistent Hypersplenism Following Portacaval Shunt. W. Va. Med. J., 59:179, 1963.
8. Hallenbeck, G. A., Wollaeger, E. E., Adson, M. A. and Gage, R. P.: Results After Portal-Systemic Shunts in 120 Patients with Cirrhosis of the Liver. Surg. Gyncol. Obstet., **116**:435, 1963.
9. LaCombe, M. and Vayasse, J.: Arguments in Favor of Splenorenal Anastomosis. J. Cardiovasc. Surg., 8:142, 1967.
10. Liebowitz, H. R.: Splenomegaly and Hypersplenism Pre- and Post-Portacaval Shunt. N. Y. State J. Med., 63:2631, 1963.
11. Linton, R. R.: Splenorenal or Portacaval Shunt? Surg. Gynecol. Obstet., **121**:117, 1965.
12. Linton, R. R., Ellis, D. S. and Geary, J. E.: Critical Comparative Analysis of Early and Late Results of Splenorenal and Direct Portacaval Shunts Performed in 169 Patients with Portal Cirrhosis. Ann. Surg., **154**:446, 1961.
13. Longmire, W. P., Jr.: Portal Hypertension. Introduction. Curr. Probl. Surg. Vol. 3-4, July, 1966.
14. Mikkelson, W. P., Edmondson, H. A., Peters, R. L., Redeker, A. G. and Reynolds, T. B.: Extra- and Intrahepatic Portal Hypertension Without Cirrhosis (Hepatoportal Sclerosis). Ann. Surg., **162**:602, 1965.
15. Mulder, D. G.: Selection of Shunt Procedures in Portal Hypertension *in* Longmire, W. P., Jr. Portal Hypertension Curr. Probl. Surg., Vol. 3-4:58, July, 1966.
16. Panke, W. F., Rousselot, L. M. and Burchell, A. R.: A Sixteen-year Experience with End-to-side Portacaval Shunts for Variceal Hemorrhage. Ann. Surg., **168**;957, 1968.
17. Redetzki, J. E., Bickers, J. N., Samuels, M. and Sekinger, D. J.: Progressive Hypersplenism After Portacaval Anastomosis. Am. J. Dig. Dis., **12**:88, 1967.
18. Sedgwick, C. E., Poulantzas, J. K. and Miller, W. H.: Portasystemic Shunts in 102 Patients with Portal Hypertension. N. Engl. J. Med., **274**:1290, 1966.
19. Talner, L. B., Boyer, J. L. and Clemett, A. R.: Intrahepatic Portal Vein Occlusion. A Cause of Portal Hypertension. Radiology, **92**:1265, 1969.
20. Tisdale, W. A., Klatskin, G. and Glenn, W. W. L.: Portal Hypertension and Bleeding Esophageal Varices: Their Occurrence in the Absence of both Intrahepatic and Extrahepatic Obstruction of the Portal Vein. N. Engl. J. Med., **261**:209, 1959.
21. Voorhees, A. B., Harris, R. C., Britton, R. C., Price, J. B., and Santulli, T. V.: Portal Hypertension in Children: 98 Cases. Surgery, **58**:540, 1965.
22. Warren, W. D., Fomon, J. J. and Zeppa, R.: Further Evaluation of Selective Decompression of Varices by Distal Splenorenal Shunt. Ann. Surg., **169**:652, 1967.

Early Respiratory Insufficiency in Acute Pancreatitis

JOHN H. C. RANSON, B.M., B.CH., DANIEL F. ROSES, M.D.,
SIMON D. FINK, M.D.

From the Department of Surgery, New York University Medical Center, New York, New York 10016

THE OCCURRENCE of respiratory failure and thoracic complications in patients with acute pancreatitis has been well documented on the basis of clinical and radiographic examination.[2,6,8,16,19] Frequently described pulmonary signs and symptoms accompanying this disease include pleural effusion, atelectasis, pneumonitis, elevated diaphragms, empyema and pulmonary infarction. The value of roentgen examination of the chest has been emphasized.[19] However, experimental evidence has suggested that respiratory mechanics and gas exchange may undergo alterations in acute pancreatitis despite an absence of changes on physical or roentgen examination,[3,12] and recent reports have emphasized the necessity of arterial blood gas determinations in assessing respiratory function.[1,18] This study was undertaken to define the frequency and prognostic significance of early respiratory insufficiency in acute pancreatitis on the basis of arterial blood gas measurements.

Materials and Methods

Patient Population: Sixty-eight patients with a clinical diagnosis of acute pancreatitis were seen on the surgical service at New York University and Bellevue Hospital Medical Centers over a 12-month period ending March 31, 1972. This report is based on a study of 40 of these patients in whom arterial blood gas determinations were carried out during spontaneous respiration on room air within 48 hours of admission or diagnosis.

The diagnosis rested on the clinical picture, hospital course and elevated serum amylase levels in all patients. It was confirmed at laparotomy or autopsy in 12 patients. Arterial blood gas determinations were carried out using freshly drawn heparinized blood which was obtained anaerobically. All the blood gas determinations were carried out prior to anesthesia or operation except in two patients who developed postoperative pancreatitis. Chest X-rays were carried out on all patients during the first 48-hour period.

Patient Population: There were 35 men and five women. The mean age was 42 years with a range of 20 to 92 years. Pancreatitis was associated with alcoholism in 33 patients and with biliary tract disease in four patients. It developed postoperatively in two patients and was idiopathic in one patient. Twenty patients had known previous attacks of pancreatitis. Seven patients (17.5%) died.

Treatment consisted of nasogastric suction, intravenous fluids and antibiotics in all cases. Most patients had indwelling urethral catheters to monitor urine output, and in many patients central venous pressures were monitored. Anticholinergics were not administered routinely.

Results

The mean initial recorded arterial pH was 7.46 ± 0.08 (standard deviation) and P_{CO_2} was 31.0 ± 6.6 mm. Hg. The mean lowest arterial P_{O_2} recorded during the first 48 hours was 71.2 ± 12.4 mm. Hg. On chest X-ray, left pleural effusions were apparent in two patients and bi-basalar atelectasis was noted in one patient. In no other patients were effusions, infiltrates or atelectasis noted radiographically during this period, and in no patient was there clinical or radiographic evidence of pulmonary edema noted. The patients were divided into

---

Submitted for publication June 6, 1972.

This work was supported in part by a grant from the Billy Rose Foundation, New York, New York.

Reprint requests: Dr. Ranson, New York University Medical Center, 550 First Avenue, New York, New York 10016.

TABLE 1. *Features of Patients in Group I, in Whom the Pa_{O_2} below 75 mm. Hg was Recorded and in Group II, in Whom the Pa_{O_2} was above 75 mm. Hg in the First 48 Hours (± standard deviation).*

	Group I $Pa_{O_2} < 75$ mm. Hg	Group II $Pa_{O_2} > 75$ mm. Hg
Number of patients	23	17
Mean Age (yr.)	42.8 ± 12.3	42.5 ± 8.4
Per cent Mortality	17.4	17.8
Per cent Undergoing Operation	34.8	17.8
Mean 48-hour low Pa_{O_2} (mm. Hg)	63.1 ± 9.1	82.1 ± 6.1
Mean Initial Arterial pH	7.48 ± 0.08	7.43 ± 0.07
Mean Initial Pa_{CO_2} (mm. Hg)	30.2 ± 7.2	32.6 ± 5.7
Mean 48-hour high serum amylase (Somogyi Units)	1063 ± 830	1336 ± 1237
Mean 48-hour low serum calcium (mg./100 ml.)	8.9 ± 1.4	9.3 ± 1.8
Mean 48-hour intravenous fluids (ml.)	9256 ± 2123	9101 ± 2111
Number Alcoholic (%)	20 (87)	12 (71)
Number Biliary (%)	2 (9)	3 (18)
Number Postoperative (%)	1 (4)	1 (6)
Number Idiopathic (%)	—	1 (6)
Number with known previous pancreatitis (%)	9 (39)	11 (65)
Number with abnormal chest X-ray in first 48 hours (%)	2 (9)	1 (6)
Number with late pulmonary complication (%)	8 (38)	3 (18)

two groups. Group One included those patients in whom a PaO_2 below 75 mm. Hg was recorded within the first 48 hours, and Group Two included those patients in whom PaO_2 was above 75 mm. Hg. Table 1 shows a comparison of these two groups. Two patients in Group One died within the first 4 hospital days. Respiratory failure was the immediate cause of death in one of these patients. The mortality rate and the mean age, highest serum amylase, lowest serum calcium and total administered intravenous fluid volumes during the first 48-hour period were similar in the two groups. The incidence of operation was 34.8% in Group One, and 17.8% in Group Two. The incidence of late respiratory complications was higher in Group One, and known previous episodes of pancreatitis were more common in patients in Group Two. The great majority of patients in this series had pancreatitis associated with alcoholism, but respiratory insufficiency was also seen in pancreatitis associated with other etiologies.

The patients were divided retrospectively into four groups on the basis of their overall clinical course as follows:

Group A, mild attack, requiring not more than 4 days of nasogastric suction followed by uneventful recovery.

Group B, moderate attack, with slow resolution requiring more than 4 days of naso-gastric suction or followed by the development of a pseudocyst or small pancreatic abscess.

Group C, severe attack requiring at least 1 week in the intensive care unit.

Group D, catastrophic attack, with rapid deterioration and progressive abdominal distension and rigidity. All patients in Group D underwent operation within 12 hours and pancreatic hemorrhage and apparent necrosis was encountered.

Figure 1 documents the lowest arterial Po_2 recorded in these 40 patients during the first 48 hours relative to their overall clinical course. The distribution of the 28 patients with acute pancreatitis seen during this time in whom arterial blood gas determinations on room air were not recorded is shown at the bottom of the figure.

It is apparent that while there is a tendency for more seriously ill patients to have lower arterial Po_2 values in the early part of their disease, several patients whose overall clinical course was not severe exhibited marked hypoxia during this period. The mean lowest arterial Po_2 in the first 48 hours was 72.0 ± 10.7 (SD) mm. Hg in those who survived and 64.1 ± 15.2 (SD) mm. Hg in those who died.

Late Respiratory Complications: Two patients in Group One died within the first 4 hospital days, but eight of the remaining patients (38%) in Group One and three patients (18%) in Group Two developed late pulmonary infiltrates or pleural effusions during

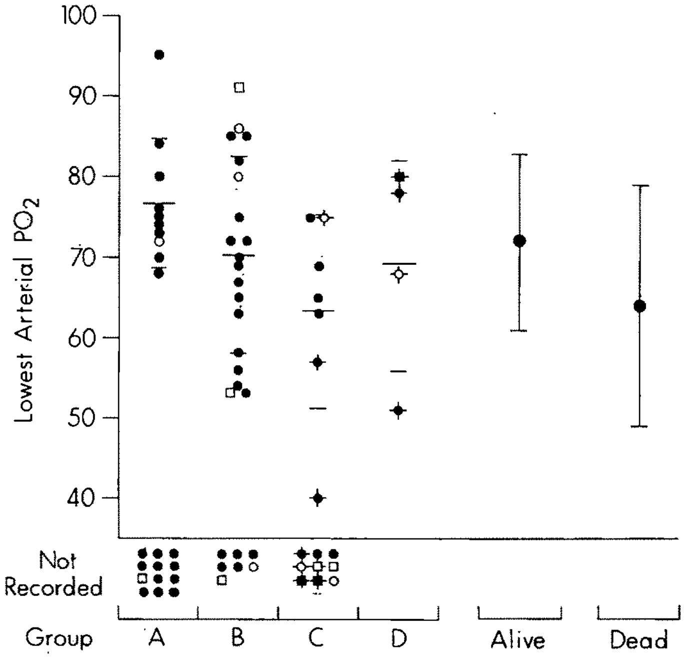


FIG. 1. Lowest recorded Pao_2 in first 48 hours in patients whose overall clinical course was: A, mild; B, moderate; C, severe; D, catastrophic. Crossbars show mean (± standard deviation) for each group and for those who did and did not survive.
Etiology of pancreatitis is indicated as follows: ●, alcoholic; ○, biliary; ■, postoperative and □, other. + indicates death.

their hospital course. Four of these patients required tracheostomy and mechanical respiratory assistance for from 3 to 5 weeks. Three (27%) of these 11 patients died. Respiratory failure was the immediate cause of death in one of these patients and a major contributing cause in the other two. However, all three patients also had severe intra-abdominal sepsis.

Four of the eight patients in Group One and two of the three patients in Group Two who developed late respiratory complications underwent early operation. It is probable that respiratory failure may have been exacerbated by anesthesia and operation. However, both the patients in Group Two exhibited mild respiratory alkalosis prior to operation and pancreatic hemorrhage and necrosis were encountered at operation.

Discussion

In 58% of this group of patients with acute pancreatitis, a mild to moderate degree of respiratory insufficiency was detected within the first 48 hours by arterial blood gas measurements. It was characterized by arterial hypoxia and a mild respiratory alkalosis. During this period, clinical evidence of respiratory distress was obvious in only two patients (5%), and radiographic evidence of effusion, atelectasis or infiltrate was noted in only three patients (7.5%). As shown in Figure 1, there was a tendency for early arterial hypoxia to be related to more severe pancreatitis, but low arterial P_{O_2} values were encountered in a number of patients who had clinically mild pancreatitis.

The occurrence of pulmonary complications and respiratory failure during the course of acute pancreatitis has been well recognized. Enquist[4] has reported pleural effusion in 25%, atelectasis in 12%, pulmonary edema in 49% and bronchopneumonia in 20% of patients with acute pancreatitis found at autopsy.

Abnormal physical findings on examination of the lungs have been reported in 30% of patients with acute pancreatitis.[2] Radiographic abnormalities consisting of effusion, atelectasis or infiltrates are reported in 14.2 to 15% of cases[6,10] and this figure rises to 45, to 61%[2,9,19] if elevation of the diaphragms is included. Eleven (28%) of the patients in this series had effusion, atelectasis or infiltrates evident on chest X-ray at some time during their hospital course.

Gliedman[7] has reported that respiratory failure appeared to be the major cause of death in 21% and contributed to a further 39% of deaths from acute pancreatitis. In the present series of patients, respiratory failure was the immediate cause of death in two (29%) and contributed directly to a further two (29%) of the seven deaths.

Pathogenesis: Respiratory insufficiency occurring in acute pancreatitis has been attributed to retroperitoneal edema, elevation of the diaphragms and abdominal distension, pain and guarding.[5,12,14] The occurrence of pleural effusions[5,8,19] may cause additional impairment of ventilatory mechanics. Further, the intravenous infusion of large volumes of fluid, as were administered in these patients, has been implicated in the pathogenesis of pulmonary insufficiency.[11] In no patient in this group was there clinical or radiographic evidence of fluid overload and, as shown in Table 1, it was not possible to relate the occurrence of early arterial hypoxia to the volume of fluids administered. Bolooki[3] has demonstrated changes in respiratory mechanics and gas exchange following the induction of experimental acute pancreatitis. In 1946 Schiepatti and Vernengo[8] showed pleural reaction following the intravenous injection of pancreatic enzymes. Zieve[20] has measured elevated serum levels of lecithinase in patients with acute pancreatitis and the infusion of lecithinase into experimental animals has been shown to be associated with altered pulmonary surface properties.[12] The high incidence of arterial hypoxia in early acute pancreatitis when compared with that in the population of a general surgical service[15] and the fact that arterial hypoxia could not be correlated with abdominal signs or fluid therapy may be related to the proposed role of circulating pancreatic enzymes in the respiratory failure seen in these patients.

The pulmonary findings reported at autopsy by Gliedman[7] in patients dying with respiratory failure in acute pancreatitis were heavy lungs with pulmonary capillary congestion and diffuse microscopic areas of atelectasis. These findings were constant and unrelated to the degree or type of pancreatic disease. Other reported autopsy findings include pleural effusion, bronchopneumonia and pulmonary emboli.[4,10]

Prognostic Significance: Previous reports have indicated that the occurrence of pulmonary complications is associated with a poor prognosis.[5,6,9] In the present group of patients, three of the 11 patients (27%) who developed clinically or radiographically apparent pulmonary complications died. Further, it can be seen from Figure 1 that there was a tendency for the occurrence of early arterial hypoxia to be associated with more severe disease. However, in the individual patient, early arterial hypoxia was of little prognostic significance as to the course of the pancreatitis and the overall mortalities in Group I and Group II were equal.

Clinical Implications and Management: The frequent occurrence of marked early arterial hypoxia in patients with acute pancreatitis which may appear to be mild and in the absence of clinically apparent respiratory distress, indicate that arterial blood gas values should be measured in every patient with acute pancreatitis during the early part of their disease. Often these patients are alcoholic and the occurrence of agitation and restlessness secondary to cerebral hypoxia may be attributed to delirium tremens. Sedation of such a patient may easily be lethal. The insidious nature of respiratory failure in these patients is unfortunately demonstrated by one patient in this series (H.R.). He was a 32-year-old chronic alcoholic admitted with epigastric pain, nausea, and vomiting. He had moderate epigastric tenderness and guarding. The respiratory rate was 28 per minute, but there were no other positive findings on physical examination of the chest or on routine chest X-ray. The serum amylase was 300 Somogyi Units % and Calcium 10.4 mg/100ml. His admission arterial blood gas values were pH, 7.63, Po_2 83 mm. Hg and Pco_2 19 mm. Hg during spontaneous respiration on room air. Over the next 24 hours, he was managed by nasogastric suction, the administration of 3,500 cc. of intravenous fluid, and antibiotics. There was a marked improvement in his pain and a decrease in the abdominal tenderness and guarding. Twenty four hours after admission, arterial pH was 7.40, Po_2 60 mm. Hg and Pco_2 20 mm. Hg on room air. Administration of oxygen (6 liters per minute) by face mask raised arterial Po_2 to 83 mm. Hg. Chest X-ray and physical examination of the chest remained unremarkable. During the second 24 hours, his general clinical improvement continued, but at 48 hours from admission, Pao_2 on room air had fallen to 57 mm. Hg.

Four hours later, the patient became agitated and restless and shortly thereafter, cardiac arrest occurred and resuscitation was unsuccessful. Autopsy revealed acute pancreatitis with 250 cc. of ascitic fluid. There were small bilateral pleural effusions. The lungs were heavy and congested with areas of atelectasis and infarction. By the usual clinical criteria and at autopsy, this patient had rather mild acute pancreatitis. He appeared to be responding well to treatment and only the arterial blood gas measurements indicated the severity of his rapidly progressive acute respiratory insufficiency.

In the great majority of cases in this series, respiratory treatment has consisted only of the administration of oxygen by face mask or nasal catheter, close observation and respiratory physiotherapy. In most instances improvement in respiratory status was seen by the third to fifth hospital day. Tracheostomy and long-term mechanical ventilatory support was required in four patients. Two patients in this series have been managed by the administration of salt poor albumen and diuretics as described by Skillman[17] and advocated by Zuidema.[21] In both patients, a reversal of progressive respiratory deterioration was seen following institution of this therapy.

These observations indicate that respiratory insufficiency is a frequent early feature of acute pancreatitis. Factors which may be implicated in its pathogenesis include impaired ventilatory mechanics secondary to abdominal pain and distension or pleural effusion, circulating pancreatic enzymes, and the infusion of large volumes of intravenous fluids. Clinical or radiographic evidence of pulmonary complications during this phase of the disease is infrequent and in most patients, the diagnosis is apparent only by arterial blood gas measurements. We believe that a number of early deaths in acute pancreatitis are related to undetected respiratory failure and that arterial blood gas measurements have an essential role in the early management of every patient with acute pancreatitis, no matter how mild the attack may appear clinically. In most patients, close observation with serial arterial blood gas measurements, oxygen therapy, respiratory physiotherapy and management of the underlying pancreatitis is the only necessary treatment. Administration of albumen and diuretics may be helpful, especially in patients requiring large volumes of intravenous fluid. In a few patients progressive respiratory deterioration necessitates tracheostomy and mechanical ventilatory support.

The occurrence of early respiratory insufficiency has no definite prognostic significance as to the course of the pancreatitis. However, the occurrence of continued or late pulmonary complications appeared to be related to the course of the underlying pancreatitis.

Summary

The incidence and prognostic significance of early respiratory insufficiency has been examined on the basis of arterial blood gas measurements within the first 48 hours after diagnosis in 40 patients with acute pancreatitis.

Arterial Po_2 fell below 75 mm. Hg in 23 patients (58%). In this group, mean low arterial Po_2 was 63. 1 mm. Hg, mean arterial pH was 7.48 and Pco_2 30.2 mm. Hg. In only three patients was there clinical or radiographic evidence of pulmonary complications at this time. There was a tendency for the degree of early hypoxia to be related to the severity of the pancreatitis, but marked hypoxia occurred in some patients with mild pancreatitis. Early hypoxia did not correlate with serum amylase, serum calcium, volume of intravenous fluids administered. or overall mortality. Eventual operation (34.8%) and late pulmonary complications (38%) were more frequent after early hypoxia. The late course of respiratory insufficiency appears related to that of the underlying pancreatitis.

Early respiratory failure occurs frequently in acute pancreatitis. It is diagnosed accurately only by arterial

blood gas measurements and may be lethal if unrecognized.

References

1. Bendixen, H. H., Egbert, L. D., Hedley-Whyte, J., Laver, M. B. and Pontoppidan, H.: Respiratory Care. Saint Louis, C. V. Mosby Company, 1965.
2. Bockus, H. L., Kalser, M. H., Roth, J. L. A., Bogoch, A. L. and Stein, G.: Clinical Features of Acute Inflammation of the Pancreas. Arch. Intern. Med., **96**:308, 1955.
3. Bolooki, H., Mobin-Uddin, K., Lombardo, C. R., Jude, J. R. and Smith, M. E.: Biophysical Characteristics of Lungs in Acute Pancreatitis. Surg. Forum, **19**:371, 1968.
4. Enquist, I. F. and Gliedman, M. L.: Gross Autopsy Findings in Cases of Fatal Acute Pancreatitis. Arch. Surg., **77**:985, 1958.
5. Finley, J. W.: Respiratory Complications of Acute Pancreatitis. Am. Surg., **35**:591, 1969.
6. Fishbein, R., Murphy, G. P. and Wilder, R. J.: The Pleuropulmonary Manifestations of Pancreatitis. Dis. Chest, **41**:392, 1962.
7. Gliedman, M. L., Bolooki, H. and Rosen, R. G.: Acute Pancreatitis. Curr. Probl. Surg., pp. 16–19, August 1970.
8. Kaye, M. D.: Pleuropulmonary Complications of Pancreatitis. Thorax, 23:297, 1968.
9. Lawson, D. W., Daggett, W. M., Civetta, J. M., Corry, R. J. and Bartlett, M. K.: Surgical Treatment of Acute Necrotizing Pancreatitis. Ann. Surg., **172**:605, 1970.
10. Lukash, W. M.: Complications of Acute Pancreatitis. Arch. Surg., **94**:848, 1967.
11. Moore, F. D., Lyons, J. H., Pierce, E. C., Morgan, A. P., Drinker, P. A., MacArthur, J. D. and Dammin, G. J.: Post-Traumatic Pulmonary Insufficiency. Philadelphia, W. B. Saunders Company, 1969.
12. Morgan, A. P., Jenny, M. E. and Haessler, H.: Phospholipids, Acute Pancreatitis and the Lungs: Effect of Lecithinase Infusion on Pulmonary Surface Activity in Dogs. Ann. Surg., **167**:329, 1965.
13. Nugent, F. W., Atendido, W. A. and Gibb, S. P.: Comprehensive Treatment of Acute Hemorrhagic Pancreatitis. Am. J. Gastroenterol., **47**:511, 1967.
14. Nugent, F. W. and Zuberi, S.: Treatment of Acute Pancreatitis. Surg. Clin. N. Am., **48**:595, 1968.
15. Overfield, W. and Powers, S. R.: Arterial Oxygen Tension: Significance in the Surgical Patient. Surgery, **71**:1, 1972.
16. Roseman, D. M., Kowlessar, O. D. and Sleisenger, M. H.: Pulmonary Manifestations of Pancreatitis. N. Engl. J. Med., **263**:294, 1960.
17. Skillman, J. J., Parikh, B. M. and Tanenbaum, B. J.: Pulmonary Arteriovenous Admixture: Improvement with Albumin and Diuresis. Am. J. Surg., **119**:440, 1970.
18. Spencer, F. C.: Blood Gas Monitoring in the Operating Room and Recovery Room. Ann. Surg., **167**:143, 1968.
19. Stein, G. N., Kalser, M. H., Sarian, N. N. and Finkelstein, A.: An Evaluation of the Roentgen Changes in Acute Pancreatitis: Correlation with Clinical Findings. Gastroenterol., **36**:354, 1959.
20. Zieve, L. and Vogel, W. C.: Measurement of Lecithinase A in Serum and other Body Fluids. J. Lab. Clin. Med., **57**:586, 1960.
21. Zuidema, G. D., Kellum, J. M., DeMeester, T. R. and Elkins, R. C.: Respiratory Failure Secondary to Acute Pancreatitis. Presented at the Eighty-third Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, Dec 6–8, 1971.

Lesions of the Subclavian Artery:

Survey of 31 Cases with Emphasis on Steal Syndromes

MARTIN H. MCMULLAN, M.D.,* JAMES D. HARDY, M.D., F.A.C.S.**

From the Department of Surgery and University Hospital, University of Mississippi Medical Center, Jackson, Mississippi

THE SUBCLAVIAN ARTERY IS of special interest for several reasons. First, this artery supplies both muscular and neurologic areas. Secondly, it arises differently on the two sides. Thirdly, it is relatively inaccessible and requires a more sophisticated approach than do most peripheral arteries. This report presents a survey of 31 patients in whom arterial lesions presented a wide range of clinical findings (Table 1).

It is useful to divide into four principal categories the pathologic entities which involved the subclavian arteries:

(1) Congenital anomalies
(2) Traumatic lesions
(3) Ischemia due to musculoskeletal disorders
(4) Atherosclerotic occlusive disease

Congenital Anomalies

The congenital anomalies included vascular ring, congenital atresia with subclavian steal, and congenital arterio-venous malformation. Congenital abnormalities of the aortic arch and its major branches may result in the formation of vascular rings around the trachea or esophagus with varying degrees of compression. The more common anomalies include double aortic arch, and anomalous innominate, left carotid or right subclavian artery.

Case Reports

Case 1. *Anomalous Right Subclavian Artery.* A 4-month-old baby was first seen by his local physician for pneumonitis and respiratory stridor at 1 month of age. With persistence of symptoms a barium swallow X-ray revealed posterior esophageal constriction. Three days following admission to the University Hospital he became hypoxic from tracheal compression and sustained cardiac arrest. Resuscitation was successful and he was operated upon immediately through a left thoracotomy incision. An anomalous right subclavian artery was exposed, arising from the descending aorta and passing posterior to the esophagus (Fig. 1). The vessel was divided, recovery was uneventful, and a right radial pulse was palpable postoperatively.

Case 2. *Anomalous Right Subclavian Artery with Atherosclerotic Aneurysm.* A 64-year-old woman, on routine chest X-ray, had a right superior mediastinal mass posterior to the trachea. Investigation at another hospital included mediastinoscopy and identification of a pulsatile mass in the right superior mediastinum. She was referred to the University Hospital where an arch aortogram using the Seldinger technic revealed an aneurysm of the right subclavian artery, which apparently originated separately from the arch of the aorta. A median sternotomy incision was utilized with extension into the right third intercostal space. However, initially the artery feeding the aneurysm could not be identified. After considerable deliberation and dissection it was apparent that the large atherosclerotic aneurysm which filled the upper portion of the right hemithorax actually represented an anomalous right subclavian artery which arose in the left hemithorax from the thoracic aorta distal to the left subclavian artery (Fig. 2). The vessel passed posterior to the esophagus. The only safe course, achieved with considerable care, was to place clamps across the subclavian artery on either side of the aneurysm, then excise the lesion and oversew the ends. A vein bypass from the ascending aorta to the right subclavian artery in the neck was considered, but was omitted because of the fever which had developed following the first operation at the other hospital, reflecting possible bacterial growth in or around the large aneurysm.

The immediate postoperative course was uneventful, but progressive respiratory difficulty necessitated a tracheostomy. Thereafter she had repeated episodes of abrupt cessation of respiration

---

Submitted for publication June 8, 1972.

Aided by USPHS Grant No. 5 RO1 HE-06163.

* Resident in Surgery.

** Professor and Chairman, Department of Surgery, and Surgeon-in-Chief to the University Hospital.

without warning: one minute she would be talking with her family and the next moment she would be cyanotic and semi-comatose. The neurologic consultant suggested a highly localized brain lesion which affected the respiratory center. She gradually improved in this respect, but died suddenly 2 months postoperatively from a dissecting aneurysm of the thoracic aorta which ruptured into the pericardium.

Case 3. *Congenital Subclavian Atresia with Steal Syndrome.* An unusual case of congenital atresia of the subclavian artery with steal syndrome was discovered in a 15-year-old Indian female who had a 2-year history of pain in the right forearm, constant numbness of the right hand, and occasional unexplained syncopal episodes. On physical examination the blood pressure in the right arm was unobtainable while in the left it was 105/60 mm. Hg. An aortic arch arteriogram was performed which revealed proximal obstruction of the right subclavian with retrograde filling of the vertebral artery. At operation the offending lesion was found to be congenital atresia of the proximal subclavian artery. A vein graft bypass from the right common carotid to the right subclavian established a good pulse in the right arm with complete relief of symptoms (Fig. 3).

Case 4. *Congenital Arteriovenous Malformation.* A 46-year-old woman had noted a life-long history of intermittent swelling and cyanosis of the right hand. A retrograde arch aortogram revealed an arteriovenous malformation involving the right subclavian and axillary artery with aneurysmal dilatation. All things considered, it was concluded that operative intervention was contraindicated, since the abnormality was so extensive that the arm might be jeopardized.

Traumatic Lesions

The three traumatic lesions encountered were false aneurysm, arterio-venous fistula and penetrating wound with loss of arterial substance.

Case 5. *False Aneurysm ("Pulsating Hematoma").* A 17-year-old male was stabbed in the left supraclavicular area. The left hemopneumothorax was treated successfully with closed thoracotomy tube drainage, but 14 months later he presented with a typical lateral medullary syndrome which included staggering gait, ptosis of the left eyelid, left facial numbness and dysphagia. In addition, a 3 cm. pulsatile mass with an associated bruit was present just superior to the middle third of the clavicle. An arteriogram revealed a false aneurysm of the subclavian artery distal to the origin of the vertebral artery. By means of a left supraclavicular approach the aneurysm was resected and an end-to-end anastomosis was performed (Fig. 4). The lateral medullary syndrome had apparently been caused by thrombus or embolus to the left vertebral or to the posterior, inferior cerebellar artery—though the mechanism was not clear. In any event, the neurologic symptoms gradually regressed.

TABLE 1

Congenital anomalies	3
Anomalous right subclavian (2)	
Atresia with steal (1)	
AV malformation (1)	
Traumatic lesions	6
False aneurysm (1)	
Arteriovenous fistula (1)	
Penetrating wound (4)	
Musculoskeletal disorders	9
Scalenus anticus syndrome	
Cervical rib syndrome	
Atherosclerotic occlusive disease	13
Without steal (6)	
With steal (7)	
	31

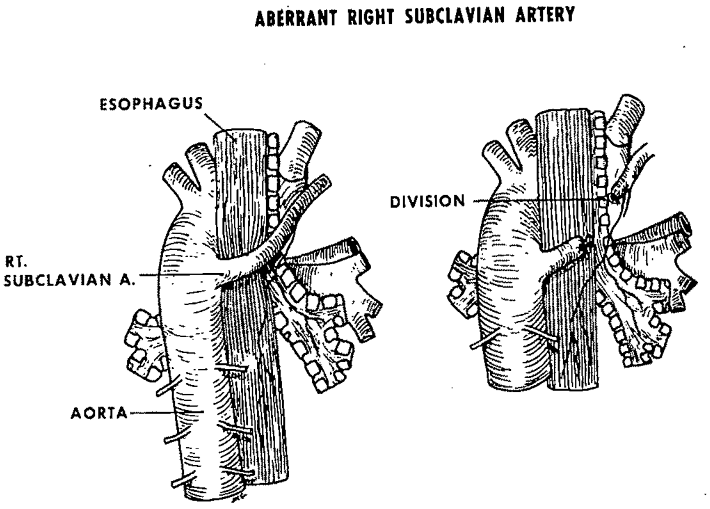


FIG. 1. Aberrant right subclavian artery causing esophageal and tracheal compression in an infant.

Case 6. *Traumatic Arteriovenous Fistula.* A 34-year-old woman was stabbed in the left supraclavicular region 15 years prior to admission. Ten years prior to admission she had noted a gradually enlarging mass in the left neck and experienced heart failure during pregnancy. She was admitted to the University Hospital with progressive dyspnea and orthopnea (Fig. 5). At operation she was found to have an arterio-venous communication between the left subclavian artery and the left innominate vein, with a false aneurysm of the subclavian artery. While under anesthesia she

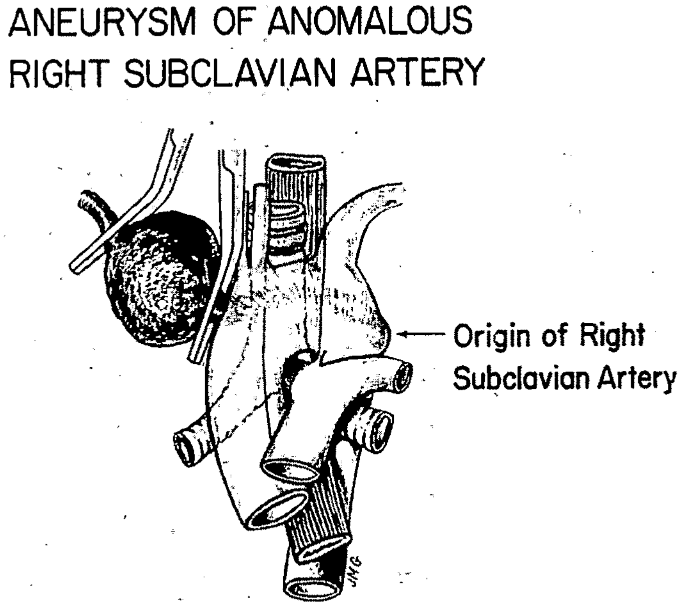

ANEURYSM OF ANOMALOUS RIGHT SUBCLAVIAN ARTERY
Origin of Right Subclavian Artery
JHG

FIG. 2 Atherosclerotic aneurysm of anomalous right subclavian artery in 64-year-old woman.

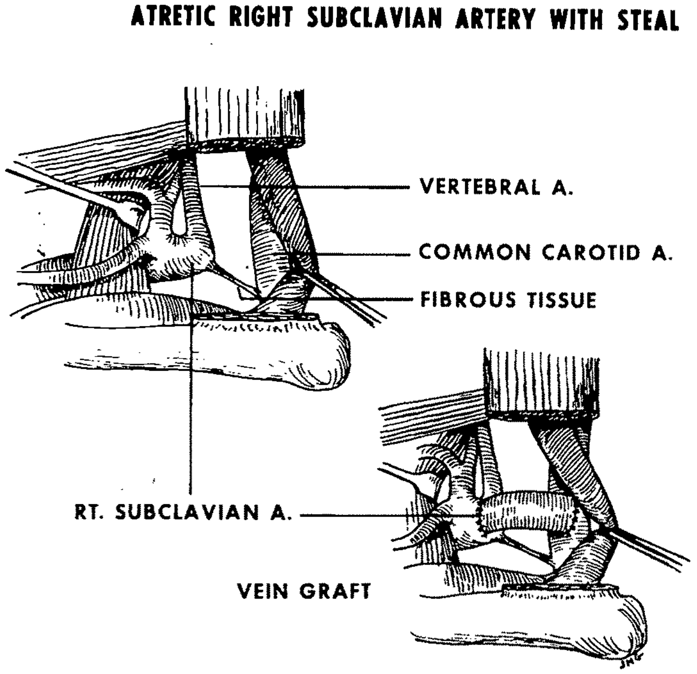


FIG. 3. Atretic right subclavian artery in 15-year-old girl with subclavian steal syndrome.

went into pulmonary edema with extreme tachycardia, and thus a quadruple ligation with excision of the internal jugular vein aneurysm and the subclavian artery aneurysm was rapidly carried out. Ideally, it would have been preferred to maintain vascular continuity, but this did not seem wise at the time. She subsequently had some coolness in the left arm but recovery was otherwise uneventful. She has since been asymptomatic.

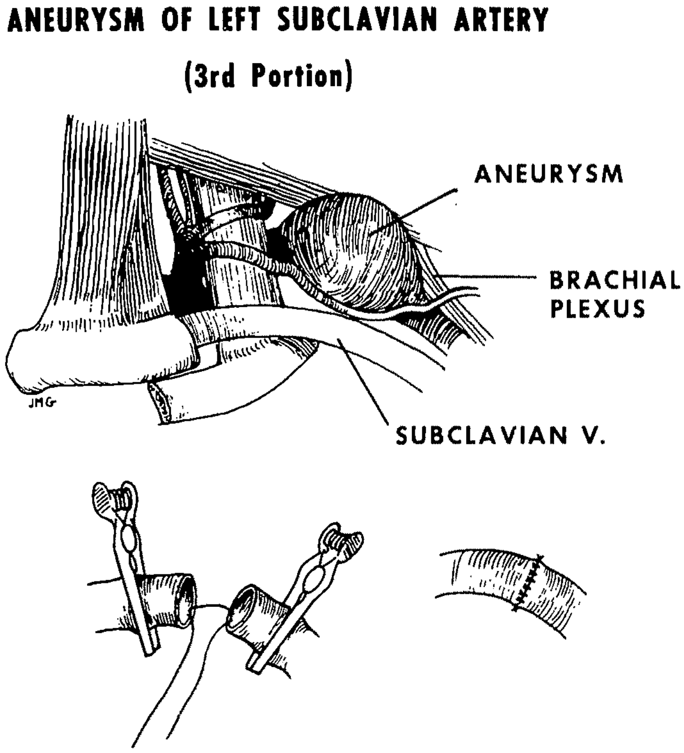


FIG. 4. Traumatic false aneurysm of left subclavian artery. Elements of the brachial plexus must be retracted gently to avoid postoperative pain and disability in the arm.

Gunshot and other penetrating wounds with or without loss of arterial substance are common in our hospitals, and the general policy is to restore continuity of all significant arteries by primary anastomosis, or by vein or prosthetic graft.

Ischemia Due to Musculoskeletal Disorders

The musculoskeletal disorders are divided into the scalenus anticus syndrome, the cervical rib syndrome and the hyperabduction syndromes due to compression by the pectoralis tendon, the first rib and other uncommon disorders. It is important to exclude nerve root compression, diaphragmatic reflex irritation, myocardial ischemia and various other causes of the shoulder-arm-hand syndrome.

Nine patients in our series had either the scalenus anticus or the cervical rib syndrome. Two subjects were believed to suffer from a combination of scalenus anticus and cervical rib pathology, and concomitantly underwent both a scalenotomy and cervical rib resection. All patients have remained asymptomatic, which attests our rather conservative approach to the diagnosis of and operation for scalenus anticus and cervical rib syndromes. However, the objective improvement in one patient was not optimal, and in this case we probably should have removed the right first rib, in addition to division of the right scalenus anticus muscle which was performed. Of course, many patients who at first appear to have thoracic outlet compression syndromes actually suffer from entirely different pathologic conditions.

Atherosclerotic Occlusive Disease

Proximal atherosclerotic occlusive lesions of the subclavian artery are conveniently divided into those with and without the subclavian steal syndrome. The symptomatology produced by an obstructing lesion in the proximal subclavian artery without steal includes paresthesias, weakness, claudication, coolness, and even cyanosis and necrosis in the involved extremity. The methods of surgical correction here are essentially identical to those utilized in the management of steal syndromes, the most common methods being endarterectomy with patch graft[14] or bypass graft. These methods will be discussed later.

Four patients with atherosclerotic occlusive disease distal to the origin of the vertebral artery were treated. These patients of course did not exhibit a subclavian steal syndrome. There were also two patients suffering from arteriosclerosis obliterans.

The Subclavian Steal Syndrome

In the subclavian steal syndrome due to proximal

TABLE 2. *Subclavian Steal Syndrome*

Causes:
1. Atherosclerosis
2. Atresia
3. Blalock-Taussig op.
4. Pressure from tumor
5. Embolus
6. Endarteritis
7. Trauma
8. Aneurysm

occlusion of the subclavian artery, the extremity symptoms are essentially the same as symptoms encountered in occlusion without steal. It is the central nervous system symptomatology which makes the syndrome unique. The retrograde flow in the vertebral artery lowers the pressure in the Circle of Willis, and the symptoms are essentially those of basilar artery insufficiency with variable degrees of syncope, headache, vertigo, blurred vision, and tinnitus. A wide range of causes responsible for the subclavian steal syndrome are listed in Table 2.

The diagnosis is suspected on the basis of the history and physical findings. It is usually confirmed by serial aortic arch aortography demonstrating the obstructing lesion, with retrograde flow in the ipsilateral vertebral artery. However, this method is at times unsuccessful. If the diagnosis is strongly suspected, one may perform additional arteriography including contralateral brachial arteriograms using pressure injection. Dye will be forced in a retrograde manner into the contralateral vertebral. The appearance of dye in the proximal ⅓ of the ipsilateral vertebral (diseased side) or, of course, in the subclavian artery distal to its obstruction proximally implies retrograde flow and a subclavian steal.

At this writing seven patients with the subclavian steal syndrome have been operated upon for correction at the University Hospital since the syndrome was described by Contorni in 1960. One case, as previously described under congenital lesions, occurred in a 15-year-old female. The six other cases occurred in adults, four females and two males, with a mean age of 54.7 years. All were apparently due to atherosclerosis, although one woman had had a diagnosis of systemic lupus erythematosus 4 years prior to operation. All were Caucasian and all lesions occurred on the left side. The most common symptoms included vertigo, tinnitus, syncope, dimming of vision, and weakness in the involved extremity. All exhibited arm blood pressure differences which ranged from 20 mm. Hg to 120 mm. Hg. The diagnosis of subclavian steal with retrograde filling of the vertebral artery on the involved side was made by arch aortography in each instance with the exception of one. The following is a report of that case.

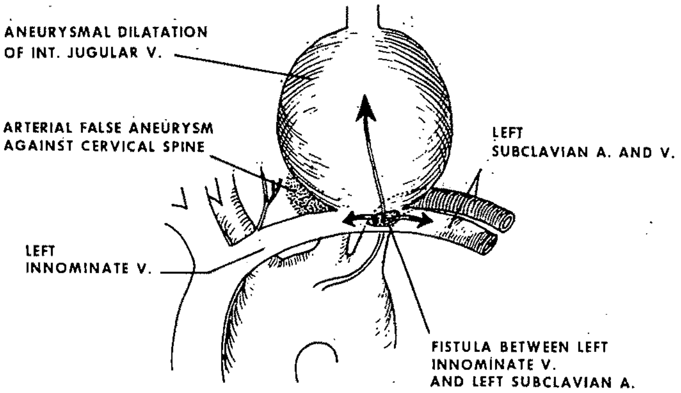

ANEURYSMAL DILATATION OF INT. JUGULAR V.
ARTERIAL FALSE ANEURYSM AGAINST CERVICAL SPINE
LEFT SUBCLAVIAN A. AND V.
LEFT INNOMINATE V.
FISTULA BETWEEN LEFT INNOMINATE V. AND LEFT SUBCLAVIAN A.

FIG. 5. Traumatic arterio-venous fistula involving left subclavian artery and left internal jugular vein and producing heart failure.

Case 7. *Subclavian Steal Syndrome.* A 60-year-old white male was seen at the University Hospital with a 7-year history of intermittent episodes of dimmed vision, vertigo, and tinnitus which recently had become more progressive and more pronounced with exercise. Physical examination revealed a blood pressure in the right arm of 160/90 and 110/90 mm. Hg in the left. A bruit was present over the left supraclavicular area and the right common carotid. Weak femoral pulses were present bilaterally but there were no pulses below. Initial laboratory data, including blood glucose and cholesterol levels, were normal.

An arch aortogram suggested proximal occlusion of the left subclavian and occlusion of the right vertebral, but revealed no retrograde flow in the left. A left retrograde brachial arteriogram showed stenosis of the left subclavian artery, an unusually large left vertebral, and a relatively small left axillary artery. There was the suggestion of asymmetrical cerebral circulation but no demonstration of actual retrograde flow could be made. However, with the classical history and physical findings, it was postulated that with arm exercise a reversal of flow in the left vertebral artery did occur, stealing from the basilar-carotid system. Therefore, an aortic to left subclavian bypass was performed utilizing a 10 mm. Dacron graft. Pressure obtained manometrically in the left vertebral prior to bypass was 90 mm. Hg and after bypass 125 mm. Hg. Postoperatively, the cuff blood pressure in the right arm was 140/70 and 120/70 in the left. On the fourth postoperative day he was noted to have a Horner's syndrome which proved to be transient, probably a reflection of trauma to the ansa subclavii. Otherwise, his course was uneventful and at this writing, 2 years postoperatively, he has had no recurrence of the neurologic symptoms.

For surgical management of the subclavian steal syndrome we have employed three different technics. The first and most physiologic is endarterectomy, with a vein or fabric patch graft, if indicated. In none of the seven patients in this series was the lesion amenable to this approach, but colleagues have used it successfully. The second approach consists of an aorto-subclavian bypass. Five patients underwent this procedure, primarily because the obstructing lesion could not be reached through a supraclavicular approach or because the obstruction was believed to be too extensive for correction utilizing endarterectomy. This procedure provides good flow in the vertebral artery and the subclavian artery distally, but it requires thoracotomy which can be inappropriate in the poor risk patient.

The last and now preferred procedure employed is a common carotid to subclavian artery shunt, using either a vein or fabric graft. The advantage of this technic is the ready accessability of these vessels without thoracotomy. The disadvantages are the possible siphoning of blood from a perhaps already diseased and atherosclerotic cerebrovascular system, and it involves some risk to a common carotid artery. The major reason for employing this procedure is that it can be done under minimal anesthesia in a poor risk patient. This method was utilized in two patients, one being the young girl with atresia of the subclavian artery in whom the cerebral vasculature was presumed to be normal. A variant of this shunt procedure is that of closing the subclavian artery as far proximally as possible, and then anastomosing the distal end of the subclavian artery to the side of the carotid artery.[12] The vertebral artery itself can be anastomosed to the carotid artery.[2]

The postoperative complications encountered in utilizing these procedures have included a transient Horner's syndrome in two patients, doubtless due to trauma to the ansa subclavii, and aorto-subclavian graft thrombosis in two patients which was treated successfully by thrombectomy under local anesthesia for exposure of the subclavian end of the graft. In still another patient infection appeared following insertion of a Dacron left carotid-subclavian artery bypass, produced secondary hemorrhage, and was successfully removed.

Discussion

The congenital anomalies of the subclavian artery which occur represent anomalies in development of the fourth aortic arch. Some of these anomalies result in vascular rings with tracheal and/or esophageal compression. In addition to a right subclavian artery arising from the descending aorta, commonly encountered vascular rings to be considered are double aortic arch, right aortic arch with left ligamentum arteriosum, anomolous distal origin of the innominate artery and anomalous left pulmonary artery.[11] The anomalous right subclavian artery arising from the descending aorta and passing posterior to the esophagus, although usually asymptomatic, may at times be life threatening and an acute emergency may arise due either to esophageal compression and subsequent aspiration or to tracheal compression. In this instance prompt surgical interruption of the compressing structure is mandatory. Fortunately most children have recurrent bouts of dysphagia, cough, stridor, wheezing, pneumonitis or atelectasis, and the diagnosis is made electively by barium swallow X-ray.

Reports of aneurysms of this anomalous vessel are exceedingly rare, according to Hunter *et al.*,[8] who have found only five in the literature including three of their own. Diagnosis of this lesion can be made preoperatively if one obtains a barium swallow X-ray showing anterior displacement of the esophagus and an arch aortogram in both the frontal and lateral projections which reveals that the subclavian artery is located posterior to the aortic arch. In our case the frontal arch aortogram gave the impression of a right subclavian aneurysm in the right upper hemithorax but revealed no clue as to the anomalous origin, resulting in confusion and delay at operation. It has been recommended by Hunter that the most advantageous approach to this lesion is through the bed of the left fourth rib, utilizing a balloon catheter for control of bleeding arising from the distal right subclavian artery. We were able to place vascular clamps proximal and distal to the aneurysm in our patient. Restoration of vascular continuity using a fabric or vein graft is preferable to simple excision, though the proximal end of the graft may be anastomosed to the arch of the aorta instead of to the stump of subclavian artery.

In separate reviews of the literature in 1968, Maranhas and associates[10] and Love[9] identified a total of 13 cases of congenital subclavian steal, including their contributions. However, in each of these cases there was present either an associated right aortic arch (10 cases) and/or coarctation of the aorta (4 cases). Of the 13 cases reported, most were symptomatic but not sufficiently so to justify operation. Apparently ours is the first case reported with isolated congenital atresia of the subclavian artery resulting in the steal syndrome. This patient showed symptoms of coolness, numbness, and pain in the right arm with occasional unexplained syncopal episodes. With angiographic evidence of the subclavian steal and rather pronounced historical data an operative approach was elected. Furthermore, since she had an apparently normal cerebrovascular tree, a carotid-to-subclavian vein bypass was employed. When recently seen in the surgical clinic, she was noted to have developed moderate aneurysmal dilatation of the vein graft. However, she remains asymptomatic and is being observed to determine if surgical intervention will become necessary, because of further enlargement of the vein graft.

Trauma to the subclavian artery can present a challenging problem in surgical approach, whether there be direct penetration, interruption, AV fistula formation or false aneurysm. The basic principles of proximal and distal control, with restoration of flow by direct repair by grafting, remain the basis of successful management, and each case must be analyzed separately. Generally, we prefer the supraclavicular incision, if suitable, with the chest prepared in the event it becomes necessary to extend the incision and split the sternum. One should not hesitate to divide the clavicle if indicated. It can usually be repaired satisfactorily but, even if not, sacrifice of clavicular length does not produce significant disability in the adult.

Musculoskeletal disorders or neurovascular compression at the superior thoracic aperture may be divided into four major categories depending upon the point of compression: (1) scalenus anticus syndrome, (2) cervical rib syndrome, (3) costoclavicular syndrome and (4) hyperabduction syndrome. We have encountered examples of 1 and 2 and have found scalenotomy or cervical rib resection or combinations of the two procedures to be effective where indicated. To our knowledge, all of these patients remain asymptomatic. We realize there are those[7,8,18] who recommend first rib resection almost routinely for these syndromes, and we too believe that this must be done in some patients to achieve complete relief of symptoms. However, in the absence of arteriographic evidence of first rib compression, scalenotomy and resection of the cervical rib if present should prove sufficient in most patients.

Since Contorni[3] in 1960 described the first case of retrograde vertebral flow supplying a proximally occluded subclavian artery, more than 200 cases of subclavian steal[13] due to various causes have been reported. The fact that not all proximally occluded subclavian arteries show reversed vertebral artery flow is undoubtedly explained by the rich collateral flow through channels such as the occipital artery, the thyrocervical trunk and the costocervical trunk.[14] However, the vertebral artery remains the most essential and certainly the most unique of the collateral routes.

Hemodynamically, Reivich *et al.*[15] showed that a reduction in subclavian pressure by only 10% of systemic arterial pressure will reverse flow in the vertebral artery. Samartino and Toole[10] demonstrated that a 50% reduction in the lumen of the subclavian artery is necessary to produce the critical 10% gradient whereby flow is reversed in the vertebral artery. In four of our cases significant stenotic or obstructive lesions were present without evidence of steal. Apparently the two factors explaining this phenomenon were the selective use of other sufficient collaterals or steriosis that did not exceed 50%.

Although a number of diagnostic studies have been proposed, Piccone and LeVeen,[14] in their excellent collective review of the subclavian steal, state that "these clinical and laboratory tests are complementary but not essential, and cannot displace the need for angiography. The certain diagnosis of a subclavian steal syndrome can be obtained only from an arch aortogram with sequential roentgenograms." Therefore, in the presence of asymmetrical pulses of the upper extremity combined with upper extremity symptoms and signs of decreased blood flow or symptoms of basilar insufficiency, arch aortography becomes mandatory.

Upon confirmation of the diagnosis of subclavian steal syndrome it then becomes necessary to determine if surgical intervention is indicated. In all seven patients reported here significant central nervous system or extremity symptoms were present, making the decision for operation a relatively easy one. In the case of the asymptomatic patient with steal or in the patient with a fixed neurologic deficit the decision favoring operation becomes much more difficult—since the natural course of the disease has not been delineated and since morbidity, mortality, and long-term results have not been investigated sufficiently in the short 10-year period since its discovery. At this writing we reserve operation for any patient with extremity or central nervous system symptoms, and we do not operate on the asymptomatic patient or the patient with a fixed neurologic deficit. Simple ligation of the vertebral artery through which the "steal" is occurring is not recommended because, first, the resulting thrombosis might extend to involve the basilar artery and, second, the blood flow to the arm is not thus improved.

In those situations, especially on the right side, where the origin of the subclavian is not as difficult to expose as on the left, an endarterectomy and patch graft carries less morbidity and is more physiologic. On the left side this may be more difficult and thoracotomy will usually be necessary for adequate exposure to permit safe proximal and distal control.

The most commonly used but not necessarily the most preferable procedure in our series was the aorto-subclavian fabric bypass. We have used this technic in patients who were considered to be good operative risks but in whom disease was too extensive for simple endarterectomy with or without patch graft, or in whom central nervous system atherosclerotic disease militated against clamping or other manipulation of the common carotid artery.

Obviously, due to the ready accessibility of the vessels, the carotid-subclavian bypass is an attractive procedure. However, considerable controversy has arisen over the use of this method because of the theoretical siphoning of blood from the carotid system. Rittenhouse and Barner[16] produced the subclavian steal experimentally and then bypassed the lesion with a vein graft from the common carotid to the subclavian artery. There was no appreciable decrease in flow in the distal carotid until exercise of the extremity was undertaken. It was then possible to measure a significant decrease in flow in the distal carotid. Studies by Dumanian[4] found decreased flow in the distal carotid under similar experimental circumstances, which was accentuated with papaverine injection into the distal subclavian. On the other hand Ehrenfeld,[5] in the experimental animal utilizing a cross-over iliac graft with unilateral proximal occlusion and an ipsilateral distal arterio-venous fistula, found that flow in a vessel proximally occluded and supplied entirely by the graft could be increased 10 fold without changing flow in the opposite distal vessel. Similar studies were obtained in a patient with subclavian steal who underwent common carotid-subclavian vein bypass. Proximal carotid flow increased from a control of 600 ml. per minute to 850 ml./min. after bypass with no change in distal carotid flow and a graft flow of 250 ml./min.

Although our indications for carotid-subclavian bypass have been in the very young with presumably normal cerebral circulation, or in the poor risk patient in whom a supraclavicular endarterectomy was not possible due to extensive disease, Piccone and LeVeen[14] have emphasized the excellent clinical results of this procedure, citing the reduced morbidity and mortality. Barner has suggested its use for left sided lesions where the nondominant arm would not be so likely to siphon blood from the cerebral circulation due to less exercise. It remains unanswered in the relatively short period of its use as to what effects this bypass procedure will have on the cerebral circulation with long-term follow-up.

Summary

Thirty-one cases of lesions involving the subclavian artery are reviewed. Four principal categories consisting of congenital anomalies, traumatic lesions, musculoskeletal disorders, and atherosclerotic disease are explored. Their symptom complexes and surgical therapy are discussed. Anomalous vessels were divided, traumatic lesions were usually corrected by direct surgical attack, generally without use of a graft, and the musskeletal abnormalities were handled by division of the scalenus anticus muscle or excision of a cervical rib when present. It is acknowledged that occasionally the first rib must also be excised for complete relief of neuro-vascular compression. Atherosclerotic occlusive disease was variously treated with endarterectomy, fabric grafts, or vein grafts. Subclavian steal syndromes have been emphasized. Although aorto-subclavian bypass was most often employed to correct atherosclerotic occlusive disease of the proximal subclavian artery, the carotid-subclavian bypass was used in the more recent cases and is now preferred.

References

1. Barner, H. B., Rittenhouse, E. A. and William, V. L.: Carotid-subclavian Bypass for Subclavian Steal Syndrome. J. Thorac. Cardiovasc. Surg., **55**:773, 1968.
2. Clark, K. and Perry, M. D.: Carotid Vertebral Anastomosis: An Alternate Technique for Repair of the Subclavian Steal Syndrome. Ann. Surg., **163**:414, 1966.
3. Contorni, L.: Il circolo collaterale vertebravertebrale nella obliterazione dell'arteria succlavia alla sue origine. Minerva Chir., **15**:268, 1960.
4. Dumanian, A. V., Frahm, C. J., Pascole, L. R., Teplinsky, L. L. and Santschi, D. R.: The Surgical Treatment of the Subclavian Steal Syndrome. J. Thorac. Cardiovasc. Surg., **50**: 22, 1965.
5. Ehrenfeld, W. K., Harris, J. D. and Wylie, E. J.: Vascular "Steal" Phenomenon: An Experimental Study. Amer. J. Surg., **116**:192, 1968.
6. Falconer, M. A. and Weddell, G.: Costoclavicular Compression of the Subclavian Artery and Vein: Relation to Scalenus Syndrome. Lancet, **2**:539, 1943.
7. Ferguson, T. B., Burford, T. H. and Roper, C. L.: Neurovascular Compression at the Superior Thoracic Aperture: Surgical Management. Ann. Surg., **167**:573, 1968.
8. Hunter, J. A., Dye, W. S., Hushang, J., Hassan, N. and Julian, O. C.: Arteriosclerotic Aneurysm of Anomalous Right Subclavian Artery. J. Thorac. Cardiovasc. Surg., **59**:754, 1970.
9. Love, J. W.: Varieties of Congenital Subclavian Steal With and Without the Syndrome. J. Thorac. Cardiovasc. Surg., **9**:358, 1968.
10. Maranhas, V., Gooch, A. S., Ablaza, S. G. G., Nakhjavan, F. K. and Goldberg, H.: Congenital Subclavian Steal Syndrome Associated with Right Aortic Arch. Brit. Heart J., **30**:875, 1968.
11. Nora, J. J. and McNamara, D. G.: Vascular Rings and Related Anomalies. *In* Pediatric Cardiology, Watson, H. (Editor). St. Louis, Mo., Mosby, 1968, p. 233.
12. Parrot, J. C.: The Subclavian Steal Syndrome. Arch. Surg., **88**:661, 1964.
13. Patel, A. and Toole, J. F.: Subclavian Steal Syndrome: Reversal of Cephalic Blood Flow. Med., **44**:289, 1965.
14. Piccone, Jr., V. A. LeVeen, H. H.: Collective Review: Subclavian Steal Syndrome. Ann. Thorac. Surg., **9**:51, 1970.
15. Reivich, M., Holling, H. E., Roberts, B. and Toole, J. F. Reversal of Blood Flow Through the Vertebral Artery and Its Effects on Cerebral Circulation. N. Engl. J. Med., **265**: 878, 1961.
16. Rittenhouse, E. A. and Barner, H. B.: Blood Flow in Carotid-Subclavian Bypass for Subclavian Steal Syndrome. Surg. Forum, **17**:399, 1966.
17. Rob, C.: Incipient Strokes: Technique of Surgical Therapy. *In* Cerebral Vascular Diseases, C. H. Millikan, R. G. Siekart, and J. P. Whisnant (Editors). New York, Grune and Stratton, 1961, p. 112.
18. Roos, D. B. and Owens, J. C.: Thoracic Outlet Syndrome. Arch. Surg., **93**:71, 1966.
19. Sammartino, W. F. and Toole, J. F.: Reversed Vertebral Artery Flow. Arch. Neurology, **10**:590, 1964.

Physiological Hemodilution:

Interrelationships Between Hemodynamics and Blood Volume After Acute Blood Loss

JOSEPH S. CAREY, M.D.,
With the technical assistance of:
HERBERT WILLIAMSON, CLARENCE MOORE, HERBERT LUNDBERG,
LEON TURNER, B.S., M.S., CALVIN SCOTT, B.S., ELLIOT SACKS

From the Thoracic Surgical Research Laboratory, Veterans Administration Hospital (Wadsworth), Los Angeles, California, and the Department of Surgery, UCLA School of Medicine, Los Angeles, California

CARDIOVASCULAR HOMEOSTASIS is temporarily maintained after hemorrhage by hemodilutional volume expansion. This process is physiologically advantageous because volume restoration is coupled with the hemodynamic advantages of hemodilution. Previous studies have shown that a decrease in hematocrit is accompanied by a rise in venous return, shifting blood to the central circulation and increasing the ratio of central blood volume to total blood volume.[3] In the presence of hypovolemia, these changes normalize cardiac output and systemic blood flow.[9]

The hemodynamic correlates of endogeneous transcapillary refilling (physiological hemodilution) after hemorrhage have not been clearly defined by previous studies. Control of the blood volume is apparently related, however, to some component of systemic or regional hemodynamics. Skillman and associates[14-17] identified activation of the renin-angiotensin system and a rise in aldosterone secretion rate after moderate hemorrhage in anesthetized dogs and conscious man. Hemodynamic changes were inconsistent except for a slight decrease in venous pressure. In the absence of consistent systemic hemodynamic alterations, it seemed likely that regional hemodynamic changes, or variations in venous pressure, might serve as volume-regulatory feedback mechanisms.

Hemodilution itself is likely to play a role in volume regulation by influencing regional hemodynamics. The present studies were designed to study the hemodynamic correlates of volume expansion during the development of physiological hemodilution after hemorrhage in the intact (unanesthetized non-splenectomized) dog. Previous studies revealed that hemodilution does not occur during the first few hours after hemorrhage in dogs anesthetized with pentobarbital.[3] Because of the possibility that interference with autonomic reflexes by anesthesia might play a role in this response,[13] the present experiments were performed under both unanesthetized and anesthetized conditions.

Methods

Anesthesia was induced by intravenous administration of sodium thiamylal (6 mg./Kg.) and sodium pentobarbital (30 mg./kg.). Polyethylene catheters were placed in the right atrium through the external jugular vein, and into the abdominal aorta through the femoral artery. Spontaneous ventilation was permitted through an endotracheal tube. Anesthesia was supplemented by administration of small doses of sodium pentobarbital (3 mg./Kg.) during the control period and for 5 hours after hemorrhage.

Cardiac output was measured by indicator-dilution technic using indocyanine green as the indicator. Fem-

---

Submitted for publication March 15, 1972.

Supported in part by U.S. Public Health Service Grant No. HE-14043-01.

Reprint Requests: Joseph S. Carey, M.D., Thoracic Surgery, Veterans Administration Hospital (Wadsworth), Wilshire and Sawtelle Blvds., Los Angeles, California 90073.

oral arterial and right atrial pressures were recorded by transducers on a photographic recorder. Blood volume was measured by dilution of ^{131}I labelled albumin, using a semi-automated blood volume computer. Hematocrit was determined from central venous blood. Arterial and venous blood samples were withdrawn for determination of pH, P_{CO_2} and P_{O_2}. Plasma protein concentration was measured by the biuret method. Serum lactate was determined by the enzymatic technic using kits supplied by Calbiochem Laboratories (Los Angeles, California). Whole blood viscosity was measured with a Brookfield cone-plate viscometer.

Control measurements were performed at 10-minute intervals during a 20-minute control period. The animals were then bled (20 ml./Kg.) over a 10-minute period. Cardiac output, intravascular pressures and blood gases were repeated 15 minutes after bleeding. Thirty minutes after bleeding, blood volume, total protein, and serum lactate were recorded in addition to hemodynamic variables. All measurements were repeated at hourly intervals for the next 4 hours. The animals were then allowed to recover. Twenty-four hours after bleeding, the animals were again anesthetized and all measurements were repeated. The withdrawn blood, exclusive of sampling volume, was then reinfused.

After an interval of 1 to 3 months, the animals were again lightly anesthetized with pentobarbital. Polyethylene catheters were placed into the right atrium through the external jugular vein, and into the carotid artery. The catheters were brought out subcutaneously in the back of the neck. Twenty-four hours later, when they had completely recovered from anesthesia, the animals were lightly restrained in a comfortable semirecumbent position on a specially constructed table. An experimental procedure identical to that described was performed.

Cardiac output and mean transit time were calculated from the Stewart-Hamilton formula using off-line computer analysis. Additional hemodynamic variables were calculated from standard formulas by the same computer program, utilizing appropriate input variables. Base excess was calculated from the Siggard-Andersen nomogram. Oxygen saturation was determined from the P_{O_2}, after correction for pH and temperature, and oxygen content was calculated from the oxygen saturation, hemoglobin (estimated from hematocrit) and P_{O_2}. Oxygen consumption was estimated by multiplying cardiac output by the arteriovenous oxygen content difference. Plasma volume and red cell volume were calculated from the total blood volume and hematocrit. The accuracy of these technics and calculations has been described in detail in previous reports from our laboratory.[4-7]

Statistical analysis was performed by calculating mean values for the results obtained in each group of experiments, and applying the *t*-test to each variable as it compared to the mean of the three control measurements.

Sampling volumes were carefully measured so that total blood loss could be calculated for each sampling period. Thus "estimated" and "measured" total blood volume were known, while estimated and measured plasma and red cell volume were determined from the hematocrit.

Results

The experimental procedure was divided into a control period and three phases after the onset of hemorrhage: Phase 1, including the 10-minute bleeding period and the subsequent 30 minutes; Phase 2, including the subsequent 4 hours; and Phase 3, the subsequent 19 hours.

Blood Volumes (Table 1, Fig. 1). At the end of Phase 1, a total of 27 ml./Kg. of blood had been removed. The measured decrease in total blood volume averaged 17 ml./Kg. in both unanesthetized and anesthetized studies indicating that 10 ml./Kg. of plasma and red cells had entered the circulation during this period. The rise in plasma volume which occurred during Phase 1 in unanesthetized studies averaged 10.8 ml./Kg./hr. With anesthesia, plasma volume rose at a rate of 7.2 ml./Kg./hr. A greater increment of red cells entered the circulation with anesthesia (5.1 ml./Kg.) than when the animals were awake (3.4 ml./Kg.).

During Phase 2, plasma volume rose at a rate of 2.4 ml./Kg./hr. without anesthesia, and additional red cells entered the circulation. With anesthesia, plasma volume increased 1.8 ml./Kg./hr. during this period and a slightly greater number of red cells entered the circulation. The plasma volume refilling rates under unanesthetized and anesthetized conditions for each experiment are listed in Table 2. Six of the nine animals showed more rapid refilling in awake studies, but the group changes were not statistically significant.

Twenty-four hours after hemorrhage, plasma volume returned to control values in anesthetized studies, and was slightly above control in awake studies. Measured red cell volume approached estimated volumes at the end of Phase 3, indicating that autotransfused red cells had left the circulation. Mean plasma volume refilling rates during Phase 3 were 0.4 ml./Kg./hr. in unanesthetized studies and 0.5 ml./Kg./hr. in anesthetized studies.

Little change in hematocrit occurred in anesthetized animals during Phase 1 and Phase 2. Without anesthesia hematocrit decreased moderately (39 to 34%) during this period. Twenty-four hours after bleeding, hematocrit averaged 28% in both groups. Changes in whole

TABLE 1. *Blood Volume and Plasma Protein Data*

Variable	Stage	Control	Phase 1	Phase 2				Phase 3
Time After Bleeding →			30 min.	90 min.	150 min.	210 min.	270 min.	24 hours
Total Blood Volume ml./Kg.	U	82.4 ± 2.1	66.1 ± 2.1**	67.9 ± 1.9**	70.2 ± 3.6**	69.6 ± 2.2**	69.9 ± 2.5**	71.9 ± 4.9**
	(E)		(55.4)				(47.4)	(45.4)
	Δ		+10.7				+22.5	+26 .5
	A	84.1 ± 3.1	67.1 ± 2.4**	70.8 ± 3.9**	70.0 ± 2.5**	70.9 ± 3.7**	69.6 ± 3.1**	70.1 ± 3.1**
	(E)		(57.1)				(49.1)	(47.1)
	Δ		+10.0				+20.5	+24.0
Plasma Volume ml./Kg.	U	49.9 ± 1.9	41.0 ± 1.6**	42.2 ± 1.8**	43.4 ± 2.5**	43.3 ± 1.4**	45.8 ± 1.7**	52.7 ± 3.8
	(E)		(33.8)				(29.0)	(27.8)
	Δ		+7.2 (10.8 ml./kg./hr.)[2]				+16.8 (2.4 ml./Kg./hr.)	+24.9 (0.4 ml./Kg./hr.)
	A	50.4 ± 2.5	39.1 ± 2.0**	42.1 ± 2.4**	41.8 ± 2.2**	41.8 ± 2.5**	41.3 ± 2.3**	50.6 ± 2.7
	(E)		(34.3)				(29.5)	(28.3)
	Δ		+4.8 (7.2 ml./kg./hr.)				+11.8 (1.8 ml./Kg./hr.)	+22.3 (0.5 ml./Kg./hr.)
Red Cell Volume ml./Kg.	U	32.6 ± 1.1	25.1 ± 1.3**	25.7 ± 1.0**	26.8 ± 1.6**	26.2 ± 1.5**	24.1 ± 1.4**	19.2 ± 1.6**
	(E)		(21.7)				(18.5)	(17.7)
	Δ		+3.4				+5.6	+1.5
	A	33.7 ± 1.2	28.0 ± 1.5**	28.7 ± 2.2**	28.2 ± 1.6**	29.1 ± 2.0**	28.2 ± 1.6**	19.6 ± 0.9**
	(E)		(22.9)				(19.7)	(18.9)
	Δ		+5.1				+8.5	+0.7
Hematocrit	U	39 ± 1	38 ± 2	38 ± 1	38 ± 1	38 ± 2	35 ± 1	27 ± 1
	A	40 ± 1	41 ± 2	41 ± 2	41 ± 2	42 ± 2	41 ± 2	29 ± 1
Whole Blood Viscosity Centipoise 23 sec^{-1}	U	5.3 ± 0.2	5.2 ± 0.4	5.1 ± 0.4	5.3 ± 0.5	5.5 ± 0.5	5.1 ± 0.4	3.6 ± 0.3*
	A	5.4 ± 0.4	6.1 ± 0.8	8.5 ± 1.2	5.4 ± 0.5	5.7 ± 0.5	5.4 ± 0.5	4.4 ± 0.4*
Plasma Protein Gm./100 ml.	U	5.6 ± 0.1	5.1 ± 0.2**	4.9 ± 0.1**	4.8 ± 0.1**	4.8 ± 0.1**	4.7 ± 0.1**	5.0 ± 0.1**
	A	5.7 ± 0.1	5.2 ± 0.1**	5.3 ± 0.2**	5.2 ± 0.1**	5.1 ± 0.1**	5.1 ± 0.1**	5.0 ± 0.1**
Total Plasma Protein Gm.	U	62.9 ± 4.3	47.0 ± 3.4**	46.5 ± 3.4**	46.8 ± 3.4**	46.8 ± 3.4**	48.4 ± 3.9**	59. ± 5.6
	(E)		(42.3)				(37.1)	(37.1)
	Δ		+4.7				+11.3	+22.2
	A	60.5 ± 2.7	42.7 ± 3.2**	46.9 ± 3.2**	45.6 ± 4.1**	44.8 ± 3.8	44.2 ± 3.7	53.0 ± 2.9**
	E		(41.2)				(36.0)	(36.0)
			+1.5				+8.2	+17.0

U — Unanesthetized (E) — Estimated

A — Anesthetized Δ — Not Change above estimated value

1. Estimated blood volumes determined by subtracting bleeding and sampling volumes from control value.
2. Refilling rates calculated from plasma volume expansion during each phase. Phase 1: 40 minutes; Phase 2: 4 hours; Phase 3: 19 hours.

* — $p < 0.05$ ** — $p < 0.01$

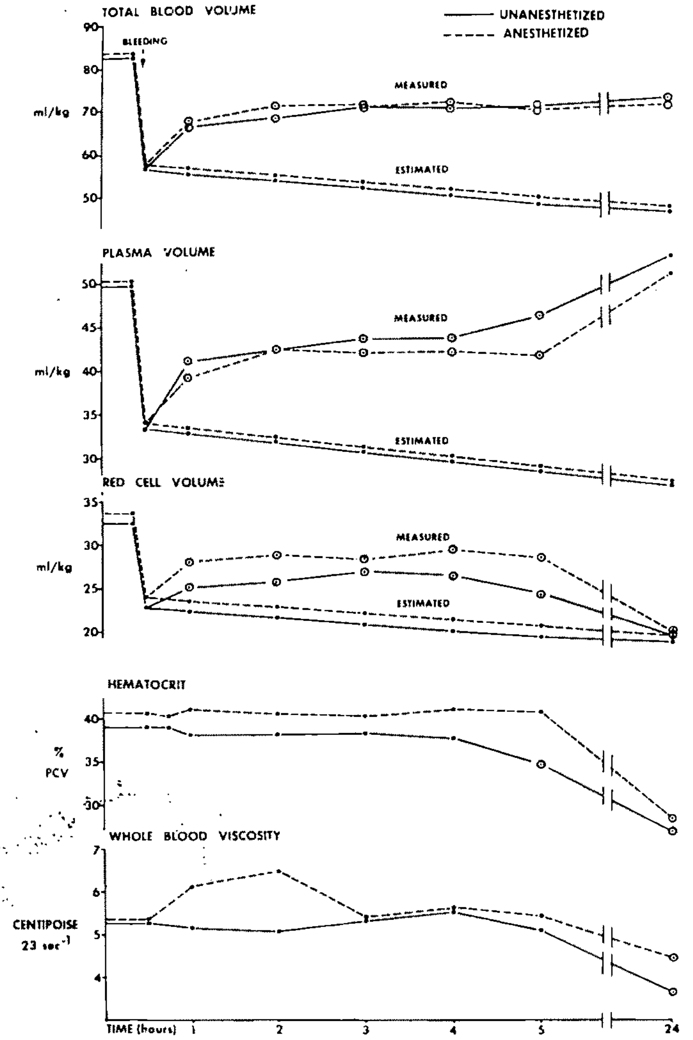


FIG. 1. Blood volume, hematocrit and whole blood viscosity after hemorrhage. Each line represents mean of nine experiments. Circled points: $p < 0.05$ as compared to control. Phase 1: from onset of bleeding to end of 1st hour; phase 2: 1 to 5 hours; phase 3, 5 to 24 hours.

blood viscosity (measured at a sheer rate of 23 inverse seconds) correlated well with changes in hematocrit.

Plasma Protein (Table 1). Plasma protein concentration was reduced at the end of Phase 1 in both unanesthetized and anesthetized studies. However, a net gain of protein occurred in both groups during this period. As plasma volume refilling proceeded during Phase 2, plasma protein concentration continued to decrease, more so in awake animals. Protein gain continued, however; at the end of Phase 2, total plasma protein had risen 11.3 Gm. above estimated loss in unanesthetized studies and 8.2 Gm. in anesthetized studies.

Twenty-four hours after bleeding, plasma protein concentration and total plasma protein remained decreased. During the first 24 hours after hemorrhage, however, a large amount of new protein entered the circulation: 22 Gm. in awake studies and 17 Gm. in anesthetized animals.

Hemodynamics (Table 3, Fig. 2–4). Cardiac output (Fig. 2) decreased to approximately the same extent after bleeding with or without anesthesia. During Phase 2, cardiac output was slightly higher in unanesthetized animals, but it remained decreased in both groups. Central blood volume remained decreased for the first 5 hours after hemorrhage in both groups. Stroke volume was higher and heart rate lower in unanesthetized studies during the control period. After bleeding, heart rate increased slightly, and stroke volume decreased markedly, in both groups.

Mean systemic arterial pressure was lower initially, and decreased more after bleeding without anesthesia (Fig. 3). Systemic resistance was also initially lower, and increased only slightly after bleeding in unanesthetized animals. With anesthesia, mean systemic arterial pressure decreased slightly, while systemic vascular resistance increased markedly and remained elevated during the first few hours after hemorrhage. Right atrial pressure did not change after bleeding with anesthesia, but decreased consistently in unanesthetized studies, remaining low during Phase 2.

Base excess decreased and serum lactate increased transiently after hemorrhage in both groups (Fig. 4). These changes were slightly more prolonged with anesthesia. Oxygen consumption showed a slight rise after bleeding in awake studies, but was decreased with anesthesia. At the end of Phase 2, oxygen consumption was moderately decreased in both groups.

Twenty-four hours after hemorrhage, hemodynamic variables had returned to control levels in unanesthetized animals. The only significant differences were a slight decrease in systemic arterial pressure and systemic vascular resistance. Mild hemodynamic changes were observed in the anesthetized group at 24 hours: tachycardia, increased systemic vascular resistance, reduced cardiac output, and decreased central blood volume.

TABLE 2. *Plasma Volume Refilling Rates*

Dog Number	Phase 1		Phase 2		Phase 3	
	U	A	U	A	U	A
0702	15.0	4.5	3.5	4.8	0.6	−0.3
0704	9.0	1.5	3.0	0.5	1.4	1.2
0708	15.0	13.5	2.0	0.2	0.8	0.0
0710	4.5	4.5	2.5	0.5	0.3	0.9
0711	4.5	16.5	3.8	1.8	0.5	0.2
0712	9.0	6.0	2.8	0.8	0.4	0.7
0714	12.0	7.5	2.0	1.8	0.0	0.9
0715	18.0	10.5	0.0	2.0	0.2	0.3
0716	9.0	11.0	3.2	1.3	−0.1	1.0

All values expressed in ml./Kg./hr.
U — Unanesthetized
A — Anesthetized

TABLE 3. *Hemodynamic Data*

Variable	Stage	Control	Time After Bleeding (Minutes) 15	30	90	150	210	270	24 Hours
Cardiac Output	U	145 ± 9**	82 ± 9**	83 ± 6**	93 ± 5**	96 ± 11**	89 ± 6**	89 ± 5**	146 ± 7
ml./Kg./min.	A	166 ± 19	85 ± 12**	93 ± 10**	99 ± 9** *	94 ± 8**	85 ± 6**	84 ± 9**	126 ± 9*
Stroke Volume	U	29 ± 2**	17 ± 2**	15 ± 1**	18 ± 2**	17 ± 2**	16 ± 2**	17 ± 2**	28 ± 2
ml.	A	19 ± 1	11 ± 2**	10 ± 1**	10 ± 1**	10 ± 1**	9 ± 1**	9 ± 1**	18 ± 1
Central Blood Volume	U	429 ± 24	285 ± 26**	282 ± 22*	300 ± 23**	293 ± 30**	292 ± 25**	280 ± 22**	417 ± 29
ml.	A	409 ± 19	304 ± 19**	305 ± 18**	303 ± 18**	298 ± 18	285 ± 15**	278 ± 16**	348 ± 23**
Right Atrial Pressure	U	3.4 ± 0.5	1.2 ± 0.3**	1.4 ± 0.4**	1.0 ± 0.3**	1.4 ± 0.4*	1.7 ± 0.4*	1.3 ± 0.3**	4.9 ± 0.6
mm./Hg.	A	3.6 ± 0.7	4.1 ± 0.7	3.7 ± 0.8	3.9 ± 0.8	3.7 ± 0.8	4.2 ± 1.2	4.0 ± 1.3	3.4 ± 0.7
Mean Systemic	U	139 ± 4	96 ± 10**	94 ± 7**	103 ± 6**	111 ± 7**	107 ± 7**	106 ± 7**	126 ± 6**
Arterial Pressure	A	166 ± 6	139 ± 10*	151 ± 9*	162 ± 8	162 ± 7	154 ± 8	152 ± 11	155 ± 6**
mm./Hg.									
Systemic Vascular	U	43 ± 3	52 ± 4*	51 ± 4	49 ± 3	55 ± 5*	54 ± 4	53 ± 2**	37 ± 2*
Resistance	A	51 ± 4	82 ± 6**	79 ± 4**	80 ± 5**	84 ± 5**	87 ± 5**	87 ± 6**	56 ± 5
mm./Hg./L./min.									
Heart Rate	U	113 ± 9	112 ± 5	128 ± 5	123 ± 8	128 ± 5	127 ± 8	124 ± 5	122 ± 7
beats/min.	A	181 ± 9	180 ± 12	188 ± 7	201 ± 5*	199 ± 6	199 ± 6	192 ± 6	152 ± 8**
Base Excess	U	4.7 ± 1.0	5.2 ± 1.0	6.4 ± 1.3	5.9 ± 0.9*	5.0 ± 0.7	5.1 ± 0.6	4.3 ± 0.9	3.4 ± 0.5
mEq/L.	A	4.9 ± 1.0	5.8 ± 1.1	7.2 ± 1.1*	5.8 ± 1.0	5.6 ± 1.0	5.6 ± 0.7	4.4 ± 0.9	5.9 ± 1.2
Serum Lactate	U	5.1 ± 0.8	—	8.4 ± 1.6	8.9 ± 0.9*	7.2 ± 0.9	4.6 ± 0.8	5.2 ± 0.6	6.8 ± 1.4
mg./100 ml.	A	9.8 ± 1.4	—	12.4 ± 1.2	15.1 ± 1.2*	12.9 ± 2.0	12.4 ± 1.9	15.2 ± 3.3	6.0 ± 0.6*
Oxygen Consumption	U	6.2 ± 0.8	6.3 ± 0.5	6.7 ± 0.7	5.9 ± 0.4	5.7 ± 0.5	5.3 ± 0.5	5.0 ± 0.5	6.0 ± 0.8
ml./Kg./min.	A	5.5 ± 0.8	4.8 ± 0.4	5.1 ± 0.5	5.1 ± 0.5	4.8 ± 0.5	4.2 ± 0.5	4.6 ± 0.6	4.2 ± 0.4

All values expressed as mean ± Standard error for each group. Control values indicate mean of three control measurements.

U—Unanesthetized * $p < 0.05$

A—Anesthetized ** $p < 0.01$

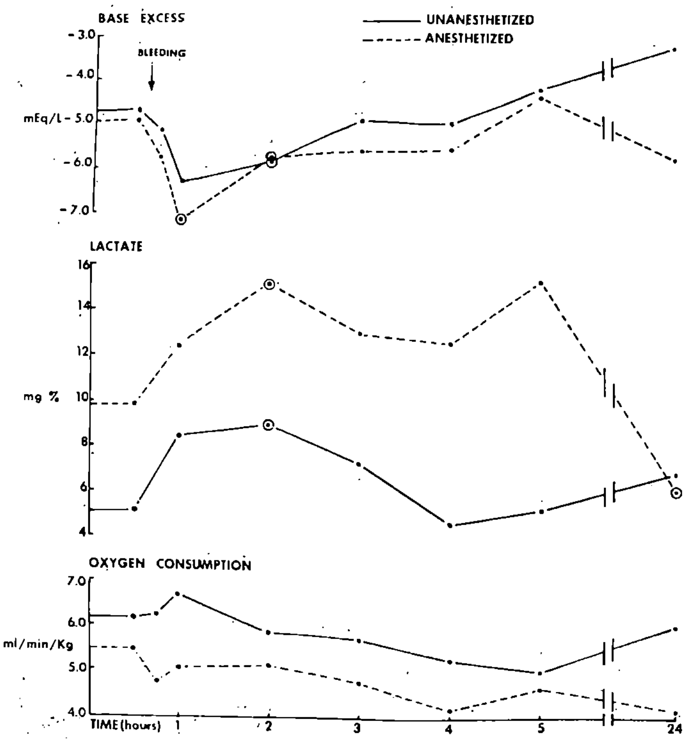


FIG. 2. Hemodynamic changes after hemorrhage. Each line represents mean of nine experiments. Circled points: $p < 0.05$ as compared to control. Phase 1: from onset of bleeding to end of 1st hour; phase 2: 1 to 5 hours; phase 3, 5 to 24 hours.

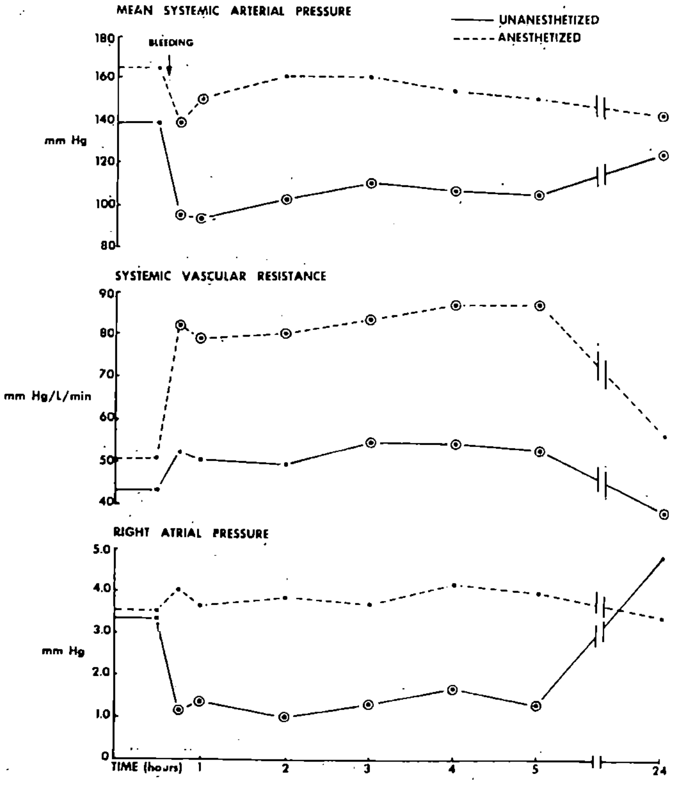


FIG. 3. Hemodynamic changes after hemorrhage. Each line represents mean of nine experiments. Circled points: $p < 0.05$ as compared to control. Phase 1: from onset of bleeding to end of 1st hour; phase 2: 1 to 5 hours; phase 3, 5 to 24 hours.

Discussion

Skillman and associates found that plasma renin activity increased immediately after a 15% hemorrhage in human volunteers[16] followed by a more gradual rise in aldosterone secretion rate. Aldosterone secretion decreased when transcapillary refill was accomplished. Cardiac output and stroke volume decrease slightly after hemorrhage, but systemic vascular resistance rose in only two of seven subjects. Central venous pressure decreased slightly but consistently. They suggested that the venous pressure response may play a role in the regulation of plasma volume refilling by serving as a volume-regulatory feedback mechanism when refilling was complete.

Winn and Lister,[18] studying splenectomized dogs, found that plasma volume expansion was delayed by removal of the kidney and inhibited completely by nephrectomy and adrenalectomy combined. These findings were reversed by the administration of angiotensin. Marks and associates[10] also found that adrenalectomy inhibited plasma volume refilling in splenectomized dogs. It is thus apparent that the kidneys and adrenals, through the renin-aldosterone mechanism, play a central role in the regulation of plasma volume.

Cope and Litwin[8] showed that thoracic duct flow increased transiently after hemorrhage in splenectomized dogs. Plasma protein concentration decreased immediately after hemorrhage. This dilution was complete within 90 minutes. This rapid refilling phase was followed by a more gradual re-expansion characterized primarily by restoration of plasma protein. These authors believed that the observed changes in thoracic duct lymph flow contributed significantly to plasma volume refilling, but other investigators have found that thoracic duct lymph flow decreases after hemorrhage.[1,2]

Skillman and associates[15] indicated that the restoration of albumin after hemorrhage comes primarily from a rise in albumin synthesis associated with a decrease in albumin catabolism, and secondarily from extravascular albumin reserves. Contributions from the thoracic duct were not needed to explain the restoration of plasma protein in their studies. Plasma protein was diluted after hemorrhage but a mean net gain plasma albumin occurred during the early post-hemorrhage period. These investigators also found that an early rapid phase volume re-expansion was followed by a slower more gradual phase. They believed, however, that the Starling phenomenon of altered capillary hydrostatic pressure was sufficient to account for transcapillary refilling during both phases.

The data of this study again reveal the phasic nature of plasma volume re-expansion after hemorrhage. The refilling rates observed during the immediate post-hemorrhagic period are far more rapid than those previously reported. McNeil and associates[11] reported refilling rates of approximately 3.5 ml./Kg./hr. in anesthetized, splenectomized dogs. In the present study, refilling rates were 4.5 ml./Kg./min. or higher in all but one experiment during Phase 1 (Table 2). These rapid refilling rates are not surprising in view of the nature of fluid exchange across the transcapillary membrane. As pointed out by Moore,[12] the resting transfer rates for water and salt across the capillary walls are extremely rapid, such that each minute the body capillaries exchange amounts of water and salt grossly in excess of those found in the entire plasma volume. In this dynamic setting the introduction of a stimulus such as acute hemorrhage is likely to produce a very rapid expansion of plasma based on the Starling mechanism alone.

Twenty-four hours after hemorrhage, the most significant change was a reduction in hematocrit and whole blood viscosity. Total blood volume was still 15% below control, but the resulting hemodilution caused a shift of blood to the central circulation, increasing central blood volume, right atrial pressure, and cardiac output. These changes are identical to those previously observed during acute normovolemic hemodilution induced by infusion of saline or dextran.[3] The blood volume may be considered as a dynamic variable which is set to maintain optimal hemodynamics. With hemodilution, a new equilibrium is established as a result of increased venous return. The central blood volume is fully restored, and systemic blood flow returns to normal. In this setting, the volume regulatory feedback function may be served by regional hemodynamic changes within the kidney. Restoration of normal renal blood flow would presumably inhibit the secretion of renin, angiotensin and aldosterone.

An important role of neuroregulation in volume control seems unlikely in view of the slight differences between volume expansion rates with or without anesthesia. The absence of a drop in venous pressure, and a lesser decrease in arterial pressure in anesthetized animals suggests that these responses, which are presumably neurogenic, are not critical factors in volume regulation. The importance of neuroregulation would be better evaluated by total pharmacologic autonomic blockade before bleeding; however, the present studies were intended to shed light on the effects of a commonly used anesthetic.

These studies clearly reveal the importance of hemodilution in the response to hemorrhage, and lend physiological support to the concept of therapeutic hemodilution, in which blood volume is supported by the infusion of colloid and crystalloid solutions after hemorrhage in man.

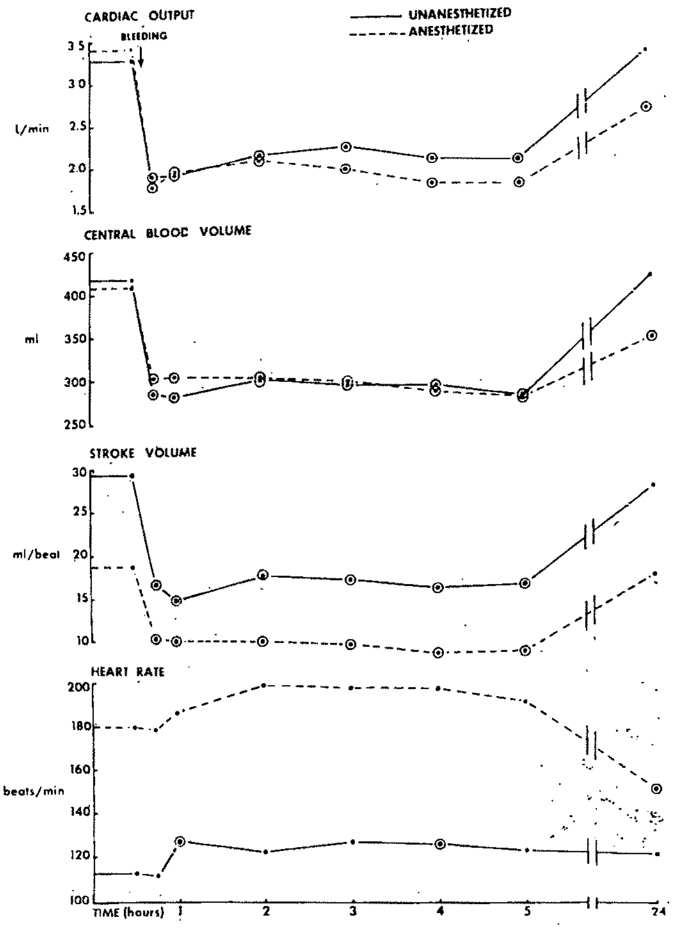


FIG. 4. Metabolic changes after hemorrhage. Each line represents mean of nine experiments. Circled points: $p < 0.05$ as compared to control. Phase 1: from onset of bleeding to end of 1st hour; phase 2: 1 to 5 hours; phase 3, 5 to 24 hours.

Summary

The interrelationships between blood volume and hemodynamics after hemorrhage were investigated in the intact dog by observing cardiovascular responses during the first 24 hours after blood loss. Nine dogs were bled (35 ml./kg.) on two separate occasions; 1) in the unanesthetized state and 2) during barbiturate anesthesia. In unanesthetized studies, plasma volume re-expansion averaged 10.8 ml./Kg. during the first hour after bleeding, 2.4 ml./Kg./hr. during the next 4 hours, and 0.4 ml./Kg./hr. thereafter. Autotransfusion of red cells occurred during the first 5 hours after bleeding; hematocrit showed little change during this time, but was decreased 24 hours after bleeding. Total blood volume increased during the first 90 minutes after bleeding, then remained constant during the remainder of the 24-hour study period. Beyond the first 90 minutes, therefore, hemodilution occurred in an isovolemic manner, by exchange of autotransfused red cells for endogenous plasma. The hemodynamic state was closely

related to changes in hematocrit and whole blood viscosity. Cardiac output, stroke volume, central blood volume and other hemodynamic variables were restored to normal values 24 hours after bleeding by virtue of physiological hemodilution, although total blood volume remained 15% below control levels.

Anesthesia did not significantly reduce the rate of plasma volume expansion. In spite of marked hemodynamic changes induced by pentobarbital (including the elimination of a decrease in venous pressure) the relationship of hemodynamic variables to blood volume remained essentially the same: blood flow was apparently more dependent on the level of hemodilution than on the degree of volume expansion.

References

1. Alicair, F. and Hardy, J. D.: Mechanisms of Shock as Reflected in Studies of Lymph of Abdominal Organs. Surg. Gynecol. Obstet. 113:743–756, 1961.
2. Berman, I. R., Moseley, R. V., Lambour, P. B. and Sleeman, H. K.: Thoracic Duct Lymph in Shock Gas Exchange, Acid Base Balance and Lysosomal Enzymes in Hemorrhagic and Endotoxin Shock. Ann. Surg., 169:202, 1969.
3. Carey, J. S.: Cardiovascular Response to Acute Hemodilution. J. Thorac. Cardiovasc. Surg., 62:103, 1971.
4. Carey, J. S., Brown, R. S., Mohr, P. A., Monson, D. O., Yao, S. T. and Shoemaker, W. C.: Cardiovascular Function in Hemorrhage, Trauma and Sepsis: Determinants of Cardiac Output and Cardiac Work. Ann. Surg., 170:910, 1969.
5. Carey, J. S., Brown, R. J., Mohr, P. A. and Shoemaker, W. C.: Cardiovascular Function in Shock Due to Hemorrhage, Trauma and Sepsis. Responses to Volume Loading and Isoproterenol Infusion. Circulation, 35:327, 1967.
6. Carey, J. S. and Hughes, R. K.: Cardiac Output: Clinical Monitoring and Management. (Collective Review) Ann. Thorac. Surg., 7:150, 1969.
7. Carey, J. S., Scharschmidt, B. F., Culliford, A. T., Greenlee, J. E. and Scott, C. R.: Hemodynamic Effectiveness of Electrolyte and Colloid Solutions for Replacement of Simulated Operative Blood Loss. Surg., Gynecol. Obstet., 131: 679, 1970.
8. Cope, O. and Litwin, S. B.: Contribution of the Lymphatic System to the Replenishment of the Plasma Volume Following Hemorrhage. Ann. Surg., 156:655, 1962.
9. Drucker, W. R., Holden, W. D., Kingsbury, B., Hoffman, N. and Graham, L.: Metabolic Aspects of Hemorrhagic Shock. II. Metabolic Studies on the Need for Erythrocytes in the Treatment of Hypovolemia Due to Hemorrhage. J. Trauma, 2:567, 1962.
10. Marks, Leon J., King, D. W. and McCarthy, H. F.: Physiological Role of Cortisol in the Plasma Volume Response to Hemorrhage. Surgery, 61:422, 1967.
11. McNeill, T. F., Dixon, J. P. and Moore, F. D.: The Effects of Hemorrhage and Hormones in the Partition of Body Water. II. The Effects of Acute Single and Multiple Hemorrhage and Adrenal Corticosteroids in the Dog. J. Surg. Res., 3: 332, 1963.
12. Moore, F. D., Dagher, F. J., Boyden, C. J., Lee, C. J. and Lyons, J. H.: Hemorrhage in Norman Man: I. Distribution and Dispersal of Saline Infusions Following Acute Blood Loss. Clinical Kinetics of Blood Volume Support. Ann. Surg., 163:485, 1966.
13. Price, H. L.: General Anesthesia and Circulatory Homeostasis. Physiol. Rev., 48:187, 1960.
14. Skillman, J. J. *et al.*: Transcapillary Refilling after Hemorrhage in the Splenectomized Dog. J. Surg. Res., 8:57, 1968.
15. Skillman, John J., Awwad, Hassan K. and Moore, Francis D.: Plasma Protein Kinetics of the Early Transcapillary Refill after Hemorrhage in Man. Surg. Gynecol. Obstet., 125:983, 1967.
16. Skillman, J. J., Lauler, D. P., Hickler, R. B., Lyons, J. H., Olson, J. E., Ball, M. R. and Moore, F. D.: Hemorrhage in Norman Man: Effect on Renin, Cortisol, Aldosterone and Urine Composition. Ann. Surg., 166:865, 1967.
17. Skillman, J. J., Olson, J. E., Lyons, J. H. and Moore, F. D.: The Hemodynamic Effect of Acute Blood Loss in Normal Man, with Observations on the Effect of the Valsalva Maneuver and Breath Holding. Ann. Surg., 166:713, 1967.
18. Win, M. S. and Lister, J.: Role of the Kidneys and Adrenals in the Homeostatic Response to Hemorrhage. Surg. Forum, 17:21, 1966.

Cerebral Metabolism and Blood Flow after Circulatory Arrest During Deep Hypothermia

AVIO M. PERNA, M.D., TIMOTHY J. GARDNER, M.D.,
KAMRAN TABADDOR, M.D., ROBERT K. BRAWLEY, M.D.,
VINCENT L. GOTT, M.D.

From the Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

THE USE OF induced hypothermia as an adjunct to surgery has been of considerable interest to surgeons for many years. Bigelow,[4] Lewis,[18] and Swan[28] reported both experimental and some clinical experience with hypothermic technics in their early cardiac surgical work in the 1950's. The clinical employment of body cooling during operation, however, has generally been confined to levels of only moderate hypothermia. Mohri, *et al.*,[8,22] and more recently Barratt-Boyes[1] have reported the use of deep hypothermia with body temperature lowered to 18 to 20° C during the surgical treatment of severe cardiac anomalies in infants. They have induced marked body cooling in these patients in order to safely accomplish complete circulatory arrest for periods of up to 1 hour.

The technic of body cooling and circulatory arrest described by Mohri differs significantly from other methods of inducing deep hypothermia in that no extracorporeal circuitry or pump is employed. Mohri's method of hypothermic surgery, used both experimentally and clinically,[7] involves the exclusive use of surface cooling and a combination of deep ether anesthesia and relative hyperventilation. As a result of the hyperventilation, very marked respiratory alkalosis develops at deep hypothermic levels and the previously common problem of ventricular irritability, seen as the body temperature falls below 25 C, is rarely encountered.

The clinical usefulness of this hypothermic technic seems to be limited not by the effects of the circulatory arrest on the heart, but by the neurologic damage which results from the prolonged circulatory arrest even at deep hypothermic levels. Mohri feels that the development of a high-stepping gait after circulatory arrest is a reliable indicator of neurologic damage in these animals. The appearance of a gait disturbance or some more serious neurologic deficits after hypothermia and arrest has enabled Mohri to define a safe time period of circulatory arrest in dogs undergoing deep hypothermia.[22,23]

In the present study, we have attempted to evaluate the effects of hypothermia and circulatory arrest on cerebral blood flow and the cerebral oxygen metabolism using Mohri's technic of hypothermia and confining the length of the circulatory arrest to what Mohri has described as a safe period. Several reports describe the effects of moderate hypothermia on cerebral metabolism[21,26] and a study by Edmunds describes the changes in cerebral metabolism after profound hypothermia and circulatory arrest using extracorporeal circuitry.[9] This paper describes the first reported attempt to study the changes in cerebral metabolism using this particular technic of induced hypothermia and circulatory arrest which does not involve extracorporeal circulation.

Methods

Ten mongrel dogs of both sexes weighing 10 to 15 Kg., with negative blood tests for filariasis, were used in this study. Atropine, 0.02 mg./Kg., was administered intramuscularly 30 minutes prior to induction of anesthesia, which was accomplished using sodium thiamylal (Surital) in a dosage of 30 mg./Kg. After insertion of a cuffed endotracheal tube, the animal was placed on a piston-type respirator, and respirations

---

Submitted for publication June 7, 1972.
Supported by USPHS Grant No. HE-09997.

were controlled at a rate of 20 cycles per minutes with an oxygen flow rate of 4-6 l/ min. The tidal volume was adjusted to maintain intratracheal pressure at 10 to 14 mm. H_2O. After the normothermic cerebral metabolic measurements were made, ether was used for anesthetic maintainence until the animal's body temperature reached 27 C. Below this temperature level, no anesthetic agent was given. The depth of anesthesia achieved with ether was sufficient to block any shivering by the animal, but was carefully maintained to avoid any cardiovascular depression. During the rewarming phase, small increments of Surital were administered in some animals as required for anesthetic maintainence. Low molecular weight Dextran, 10 cc. /Kg., was slowly administered intravenously during the cooling of the animal.

After the induction of anesthesia, arterial and venous catheters were inserted in the left femoral vessels and a silastic-coated stainless steel blood gas probe was inserted through a purse string suture into the right femoral artery. A 3 cm. diameter midline cranial defect was made and a similar blood gas probe was inserted into the sagittal sinus. A third stainless steel probe, this one coated with Teflon, was placed on the parasagittal cortical surface of the brain through a 3 mm. incision in the dura mater about 1 cm. lateral to the sagittal sinus.

The silastic coated cannulae were attached to a two-channel mass spectrometer* which, as described earlier,[5] continuously analyzes specific blood gases in amounts directly proportional to the partial pressures of the substances in the blood. This apparatus, which has been used both in clinical and experimental studies,[5,6,10] contains a high pressure vacuum pump which draws blood or tissue gases into the machine through the steel cannulae. The silastic or Teflon membranes provide both a thromboresistant surface and act as diffusion membranes, with the silastic membrane allowing nearly instantaneous diffusion of gases from the blood into the cannula and limiting its use therefore to a flowing liquid or a gaseous medium. The Teflon membrane, on the other hand, achieves a diffusion lag time, thus providing sufficient time for the constant equilibration of tissue gases around the sampling tip of the cannula. After the blood or tissue gases have been drawn into the machine, the specific substances being measured are identified and quantitated according to their molecular weights by the technic of mass spectrography.

The first mass spectrometer used in this study was constructed to measure P_{O_2}, P_{CO_2}, and P_{ARGON}. The spectrometer was connected to a two-channel recorder which provided a continuous quantitative tracing of the measured oxygen and argon levels in the femoral artery and sagittal sinus. In five of the animals in which the Teflon cannula was placed on the surface of the cerebral cortex, a second mass spectrometer, calibrated for tissue measurement of P_{O_2} and P_{CO_2}, was used for continuous monitoring of cortical oxygen and carbon dioxide levels.

After these preparations were made, the animal was given argon by inhalation at a flow rate of 1.5 l/min with oxygen administration continuing. Using argon as the inert gas and obtaining saturation-desaturation curves for argon by monitoring its concentration in the femoral artery and sagittal sinus during and after argon administration, cerebral blood flow (CBF) could then be determined using a modification of the Kety-Schmidt formula, as described earlier.[24] After determining the oxygen content of the arterial and sagittal sinus blood, the cerebral oxygen consumption ($CMRO_2$) could then be calculated. These cerebral metabolic measurements were repeated in all of the animals at body temperatures of 20 to 18 C prior to circulatory arrest and again at 36 to 38 C following arrest and after rewarming.

When the metabolic studies were completed at 20 C, a right thoracotomy was performed through the fifth intercostal space and the superior and inferior vena cavae and azygos vein were occluded, the ascending aorta was cross clamped and the respirator was stopped. Young's solution* was injected into the aortic root in amounts sufficient to produce immediate cardiac arrest, usually 2 cc./Kg. After 45 minutes of complete circulatory arrest, the venous channels were opened, the lungs were reinflated, and the aortic cross clamp was released. Gentle cardiac massage was then performed, calcium chloride was administered intravenously (300 to 500 mg.), and within 10 to 20 minutes spontaneous heart action ensued. The animal was then placed in a warm water bath and the thoracotomy closed.

After rewarming was completed and the body temperature had returned to 36 C, argon administration was again begun and the CBF, O_2(A-V) and $CMRO_2$ were measured in the same manner as above. The entire experiment required 6 to 8 hours from the induction of anesthesia to completion of the final argon study.

Results

The changes observed in the $CMRO_2$, O_2(A-V), and CBF in the ten animals are summarized in Table

---

* Medspect Model MMS-8, Scientific Research Corporation, Baltimore, Maryland.

* Young's solution: 0.81 Gm. potassium citrate, 2.46 Gm. magnesium sulfate 0.001 Gm. neostigmine methyl sulfate, water q.s. to 100 cc., pH adjusted to 7.4 with sodium bicarbonate.

TABLE 1. *Cerebral Metabolic Measurements*

	37° (Before Cooling)			20° (Before Circulatory Arrest)			37° (After Rewarming)		
Animal Number	A-V O_2* Difference	$CMRO_2$**	CBF***	A-V O_2* Difference	$CMRO_2$**	CBF***	A-V O_2* Difference	$CMRO_2$**	CBF***
1	3.65	1.03	28	2.94	0.46	16	6.38	1.41	22
2	3.38	0.85	25	1.57	0.22	14	5.22	1.25	24
3	4.70	1.36	29	2.10	0.46	22	5.75	1.78	31
4	3.48	1.12	32	2.20	0.35	16	3.42	1.19	32
5	3.82	1.22	32	2.42	0.49	20	4.20	1.09	26
6	4.80	1.52	31	2.62	0.46	17	6.57	1.65	25
7	3.08	1.54	50	1.41	0.44	31	6.68	2.21	33
8	4.35	2.81	50	2.10	0.77	37	4.01	1.64	41
9	5.20	1.92	37	2.96	0.54	18	6.82	1.97	29
10	5.30	1.91	36	2.20	0.33	15	7.22	1.87	26
Median	4.18	1.44	32	2.20	0.46	18	6.06	1.65	28
% Change				↓47%	↓69%	↓46%	↑45%	↑15%	↓18%

* Oxygen extraction expressed as cc. O_2/100 cc. blood

** Oxygen consumption expressed as cc. O_2/100 Gm. brain/minute

*** Cerebral blood flow expressed as cc./100 Gm. brain/minute

I. The median value for the cerebral oxygen consumption at 20 C decreased by 69% of the measured normothermic value, while the median oxygen extraction decreased by 47% of the observed normothermic O_2(A-V) and the CBF decreased an average of 46% of the normothermic flow rate. These changes are illustrated in Figure 1.

Measurements of oxygen consumption made after circulatory arrest and at the end of the rewarming period when the body temperature had returned to normothermic levels showed a median increase of 15% over the initial normothermic level. There was a median increase of 45% in oxygen extraction and a median decrease of 18% in the cerebral blood flow.

Table 2 summarizes the observed values for the mean systemic arterial blood pressures (MBP) and the cerebral vascular resistances (CVR) noted at the three periods of metabolic measurements. Although there were considerable variations noted in these parameters among the ten animals, a comparison of median values of MBP and CVR shows a decrease from 125 mm. Hg at 38 C to 70 mm. Hg at 20 C without any change in the CVR. Arterial P_{CO_2} values, at this time, ranged from 12 to 20 mm. Hg in the ten animals. In the post-rewarming period at a body temperature of 36 to 38 C, the median MBP was 110 mm. Hg while the median CVR had increased to 3.8. At this time, the arterial P_{CO_2} level ranged from 45 to 60 mm. Hg.

The cerebral P_{O_2} and P_{CO_2} levels monitored directly on the cortical surface during circulatory arrest in five animals are summarized in Table 3 and 4. Figure 2 represents a typical tracing of the cerebral cortical P_{O_2} and P_{CO_2} levels obtained during circulatory arrest and demonstrates the characteristic decrease in the P_{O_2} level during the first 10 to 15 minutes of arrest as well as the steady increase in the cortical P_{CO_2} level which began as the P_{O_2} level equilibrated. The mean per cent decline in the cerebral P_{O_2} level during circulatory arrest was 39% of the pre-arrest value with nearly all of this decrease being observed in the first 15 minutes of arrest. The mean per cent increase in the cerebral cortical P_{CO_2} level, on the other hand, was 163% with most of the observed increase occurring during the final 30 minutes of the circulatory arrest.

Discussion

The most significant fact to be derived from the data obtained in this study, is that cerebral oxygen consumption data obtained after circulatory arrest and rewarming demonstrate an average increase of 15% over the pre-cooling oxygen consumption values. As shown in Table 1, seven animals had an increase in oxygen consumption after hypothermia and circulatory

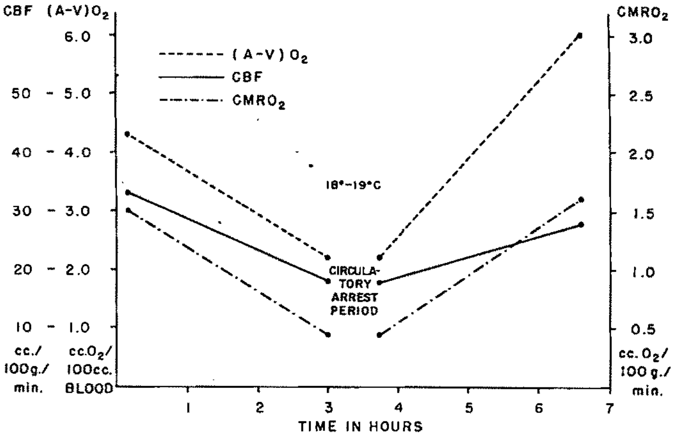


FIG. 1. Changes in cerebral metabolism during deep hypothermia.

TABLE 2.

	37° (Before Cooling)		20° (Before Circulatory Arrest)		37° (After Rewarming)	
Animal Number	MBP*	CVR**	MBP*	CVR**	MBP*	CVR**
1	115	4.7	65	4.2	110	5.0
2	130	5.2	70	5.0	120	5.0
3	125	4.3	75	3.4	125	4.1
4	85	2.7	60	3.7	65	2.0
5	125	3.9	70	3.5	110	4.2
6	125	3.9	60	3.4	115	4.6
7	140	2.8	100	3.2	120	3.6
8	130	2.6	80	2.2	100	2.4
9	115	3.1	65	3.5	90	3.1
10	110	3.1	100	6.6	75	2.9
Median	125	3.5	70	3.5	110	3.8

* Mean blood pressure in mm. Hg

** Cerebral vascular resistance expressed as mm. Hg/cc. blood/100 Gm. brain/minute

arrest, two animals showed essentially no change, while only one dog had a decline in oxygen consumption. This return of the rate of oxygen metabolism following deep hypothermia and complete circulatory arrest for 45 minutes to the pre-hypothermic CMRO$_2$ levels indicates a resumption of adequate, if not normal, cerebral metabolic activity.

Despite this return to pre-arrest levels of cerebral oxygen consumption, cerebral blood flow declined an average of 18% after hypothermia and arrest. Oxygen consumption was maintained at generally higher than pre-cooling levels by an increase in oxygen extraction from the arterial blood in the brain, as is illustrated in Figure 1. The decline in CBF as well as a slight increase in the cerebral vascular resistance in the post-hypothermic condition indicates some degree of cerebral damage as a result of deep hypothermia and the circulatory arrest. Although Dextran was administered, as Mohri had recommended,[23] intravascular coagulation in small vessels would appear to be the most likely explanation for the decline in cerebral blood flow and the increase in cerebral vascular resistance. It is noteworthy, however, that no increase in the CVR was measured in the studies performed at 20 C. and prior to the arrest, when vascular sludging from an increased blood viscosity should have been at its greatest level.

An additional explanation for the decline of the cerebral blood flow after circulatory arrest and rewarming might be the presence of some form of cerebral parenchymal damage. Factors inducing cerebral edema as well as space-occupying intracranial lesions may reduce CBF[14,16] and, although there was no evidence of the latter, some cerebral swelling may have been present in the post-arrested state. Regardless of what specific factors resulted in a fall in CBF, the most noteworthy finding in this study was the return of cerebral oxygen consumption to the normothermic control level. The capability of the brain to compensate for a decline in blood flow with an increase in oxygen extraction after the double insults of deep hypothermia and complete circulatory arrest explains the restoration of adequate cerebral metabolic activity.

In the post-hypothermic period, a decrease in the mean blood pressure as compared to the pre-cooling period was noted (Table 2). It has been demonstrated that the cerebral blood flow is unaffected by the level of systemic blood pressure provided the mean systemic blood pressure remains above 60 to 65 mm. Hg.[12,17] This fact is important when interpreting the decline of the CBF since, despite a fall of systemic blood pressure after rewarming, the decrease in cerebral blood flow at this time must be due to intrinsic cerebral factors and not the result of altered systemic hemodynamics.

A comparison of the oxygen consumption values obtained in the initial pre-cooling state with the oxygen consumption values measured at the end of the rewarming phase must take into account several variables introduced by necessity into the study. The initial cerebral metabolic measurements were made with the animals anesthetized with sodium thiamylal, a barbiturate derivative. Barbiturates are well known to affect cerebral metabolic activity, with the degree of metabolic depression related to the depth of anesthesia.[13,19,27] At the time of the post-rewarming cerebral metabolic studies, these animals were beginning to recover from the obtunded state in which they had been during rewarming. In some of the animals, small doses of sodium thiamylal were administered during rewarming, but only when the animals began to move or struggle against the respirator before com-

TABLE 3. *Cerebral P_{O_2} Measurements*

	(mm. Hg)					
	No. 1	No. 2	No. 3	No. 4	No. 5	Median
Beginning of circulatory arrest	57	100	102	106	95	100
After 15 minutes of circulatory arrest	49	68	67	75	62	67
After 30 minutes of circulatory arrest	46	66	66	60	59	60
After 45 minutes of circulatory arrest	46	66	62	59	58	59
% decrease during circulatory arrest	↓19.3%	33%	39.2%	44.4%	39%	

TABLE 4. *Cerebral P_{CO_2} Measurements*

(mm. Hg)

	No. 1	No. 2	No. 3	No. 4	No. 5	Median
Beginning of circulatory arrest	29	11	23	20	44	23
After 15 minutes of circulatory arrest	29	12	36	24	58	24
After 30 minutes of circulatory arrest	46	22	48	41	106	46
After 45 minutes of circulatory arrest	62	29	63	52	118	62
% increase during circulatory arrest	↑114%	163%	174%	160%	170%	

pletion of the rewarming. It is not possible to assess accurately how these different types of neurologic depression counterbalance when considering the effects on cerebral oxygen consumption. It is likely, however, that during the initial measurements the degree of metabolic depression was greater.

The other major variables which are present in this study involve the changes in the blood gas and pH levels before and after hypothermia. When the initial measurements were made, the arterial Po_2 and pH were higher and the Pco_2 levels were lower (Po_2 450 to 600 mm. Hg., Pco_2 40 to 45 mm. Hg, and pH 7.40 to 7.50). After rewarming, the Po_2 ranged from 150 to 250 mm. Hg despite continued 100% oxygen inhalation. The pH levels were between 7.22 and 7.34 and the Pco_2 ranged from 45 to 60 mm. Hg. Despite the reduction in the blood Po_2 levels after rewarming, the arterial oxygen saturation remained nearly 100% and the decrease in the arterial Po_2 levels should, therefore, have no effect on the $CMRO_2$. A reduction in the pH levels might have affected the post-hypothermia metabolic studies since cerebral blood flow has been shown to be greater in an acidotic state regardless of the level of the Pco_2.[14] In addition, the hypercapnia seen in all of these animals following rewarming would have produced a definite cerebral vasodilatation with a resultant increase in the CBF, as has been demonstrated both experimentally and clinically.[11,15] There was, however, a decrease in CBF at this time confirming the fact that some degree of cerebral damage must exist in the animals in the post-hypothermic state.

The changes observed in the blood pressure and the cerebral vascular resistance during the three periods of measurements are noteworthy for several reasons. The characteristic decline in the systemic arterial pressures during cooling is well established, as is the gradual decline in the pulse rate.[25] Of special interest is the lack of any increase in the cerebral vascular resistance during deep hypothermia in spite of very low arterial Pco_2 levels at that time. This finding is at variance with the observations of Edmunds, who used a pump to supply blood to the brain at a constant pulse pressure regardless of the level of body temperature.[9] At 18 to 20 C and prior to circulatory arrest in this present study, the arterial Pco_2 levels in the dogs ranged between 12 and 20 mm. Hg as a result of hyperventilation. Kety described a direct relationship between arterial carbon dioxide levels and cerebral blood flow and, because of this relationship, Belsey and others have recommended the use of hypercapnia as a means of achieving cerebral vascular dilatation during hypothermia.[2,20] Using Mohri's method of surface induced hypothermia with hyperventilation and a resultant respiratory alkalosis, arterial Pco_2 levels fell to very low levels, but despite this marked decline there was no significant change in the cerebral vascular resistance, as noted in Table 2.

The direct monitoring of cerebral cortical Po_2 and Pco_2 using the mass spectrometer during circulatory arrest provides a means of observing the basic metabolic activity of the brain during a period of prolonged anoxia. The typical pattern of change of the cortical Po_2 level

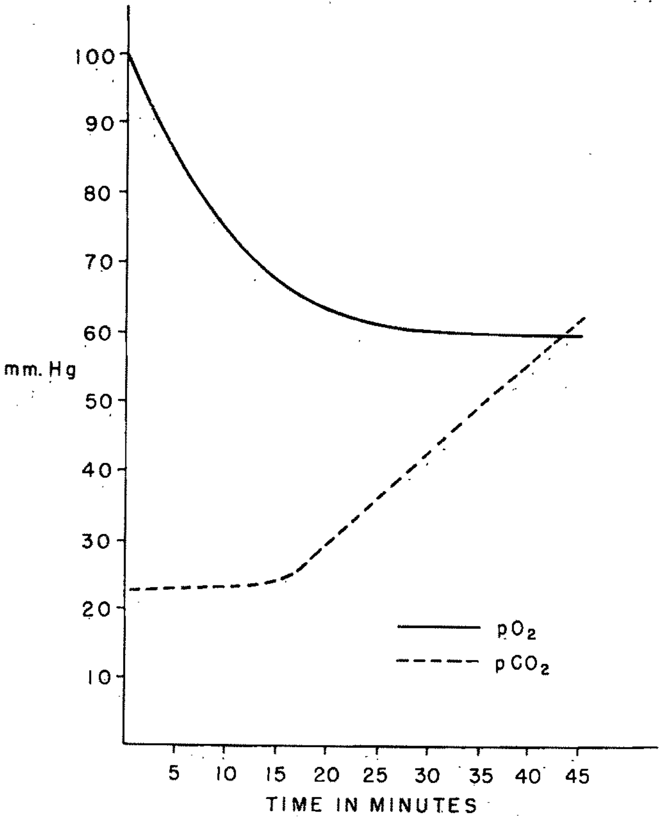


FIG. 2. Changes in cerebral cortical Po_2 and Pco_2 levels during circulatory arrest.

observed in this study, namely an early and significant decline in Po_2 followed by stabilization of the oxygen at a reduced level suggests that cerebral cortical oxygen is depleted during the initial 10 to 15 minutes of arrest. The subsequent elevation of the cortical Pco_2 level after oxygen depletion is closely similar to what occurs in the myocardium during anoxic cardiac arrest,[6,10] and the Pco_2 elevation is interpreted as being a result of anaerobic metabolism. The fact that the rate of elevation of the Pco_2 level is nearly constant during the arrest suggests a steady rate of metabolic activity in the brain despite the complete lack of circulation. Although there is no apparent correlation between the cortical gas tension changes during the circulatory arrest period and the post-arrest metabolic changes in these five animals, the direct cortical measurements do provide a means of monitoring the basic metabolic changes in the brain during the period of circulatory arrest.

Summary

1. Cerebral metabolic activity was measured in ten dogs undergoing deep hypothermia and circulatory arrest for 45 minutes using a method of surface induced cooling, ether anesthesia, and hyperventilation. Cerebral blood flow and cerebral oxygen consumption were measured utilizing a mass spectrometer by the inert gas technic.

2. Cerebral oxygen consumption at the completion of circulatory arrest and rewarming increased 15% over the mean pre-cooling rate of oxygen consumption, indicating a restoration of adequate cerebral metabolic activity. A mean decrease in the cerebral blood flow of 18% and an increase of cerebral vascular resistance of 8% in the post-arrest state was found, suggesting mild cerebral vascular damage.

3. Direct and continuous measurements of the cerebral cortical Pco_2 and Pco_2 levels during the 45 minutes of circulatory arrest in five animals indicate continuing cerebral metabolic activity during the arrest period, with brain oxygen utilization ceasing after the first 15 minutes of the arrest period.

4. Despite the marked lowering of the blood Pco_2 levels in the animals at deep hypothermic levels as a result of the hyperventilation, there was no evidence of an increase in cerebral vascular resistance.

5. Using the technic of surface induced hypothermia with ether anesthesia and hyperventilation, circulatory arrest for 45 minutes at 18 C was tolerated by the animals without evidence of impairment of cerebral metabolism, despite a consistent reduction in cerebral blood flow.

References

1. Barratt-Boyes, B. G., Simpson, M. and Neutze, J. M.: Intracardiac Surgery in Neonates and Infants using Deep Hypothermia with Surface Cooling and Limited Cardiopulmonary Bypass. Circulation, 43, Suppl. 1:25, 1971.
2. Belsey, R. H., Dowlatshaki, K. and Skinner, D. B.: Profound Hypothermia in Cardiac Surgery. J. Thorac. Cardiovasc. Surg., 56:497–506, 1968.
3. Bigelow, W. G., Lindsay, W. K. and Greenwood, W. F.: Hypothermia: Its Possible Role in Cardiac Surgery. Ann. Surg., 132:849, 1950.
4. Bigelow, W. G. and McBirnie, J. E.: Further Experience with Hypothermia for Intracardiac Surgery in Monkeys and Groundhogs. Ann. Surg., 137:361, 1953.
5. Brantigan, J. W., Gott, V. L., Vestal, M. L., Fergusson, G. J. and Johnston, W. H.: A Nonthrombogenic Diffusion Membrane for Continuous *in vivo* Measurement of Blood Gases by Mass Spectrometry. J. Appl. Physiol., 28:375, 1970.
6. Brantigan, J. W., Perna, A. M., Gardner, T. J. and Gott, V. L.: Intramyocardial Gas Tensions in the Canine Heart During Anoxic Cardiac Arrest. Surg. Gynecol. Obstet., 134:67, 1972.
7. Dillard, D. H., Mohri, H. and Merendino, K. A.: Correction of Heart Disease in Infancy Utilizing Deep Hypothermia and Total Circulatory Arrest. J. Thorac. Cardiovasc. Surg., 61:64, 1971.
8. Dillard, D. H., Mohri, H., Merendino, K. A., Morgan, B. C., Baum, D. and Crawford, E. W.: Total Surgical Correction of Transposition of the Great Arteries in Children Less Than Six Months of Age. 129:1258, 1969.
9. Edmunds, L. H. and Folkman, J.: Cerebral Metabolism During Hypothermia and Circulatory Arrest. J. Surg. Res., 1:201, 1961.
10. Gardner, T. J., Brantigan, J. W., Perna, A. M., Bender, H. W., Brawley, R. K. and Gott, V. L.: Intramyocardial Gas Tensions in the Human Heart During Saphenous Vein-coronary Artery Bypass. J. Thorac. Cardiovasc. Surg., 62:844, 1971.
11. Gibbs, F. A., Maxwell, H. and Gibbs, E. L.: Volume Flow of Blood Through the Human Brain. AMA Arch. Neurol. Psych., 57:132, 1947.
12. Hafkenschiel, J. H., Crumpton, C. W., Shenkin, H. A., Mayer, J. H., Zintel, H. A., Wendel, H. and Jeffers, W. A.: The Effects of 20° Head-up Tilt upon the Cerebral Circulation of Patients with Arterial Hypotension Before and After Sympathectomy. J. Clin. Invest., 30:793, 1951.
13. Homburger, E., Himwich, W. A., Etsten, B., York, G., Maresca, R. and Himwich, H. E.: Effect of Pentothal Anesthesia on the Canine Cerebral Cortex. Am. J. Physiol., 147:343, 1946.
14. Kety, S. S.: Circulation and Metabolism of the Human Brain in Health and Disease. Am. J. Med., 8:205, 1950.
15. Kety, S. S. and Schmidt, C. F.: The Effects of Altered Arterial Tensions of Carbon Dioxide and Oxygen on Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men. J. Clin. Invest., 27:484, 1948.
16. Kety, S. S., Shenkin, H. A. and Schmidt, C. F.: The Effects of Increased Intracranial Pressure on Cerebral Circulatory Functions in Man. J. Clin. Invest., 27:493, 1946.
17. Lassen, N. A.: Cerebral Blood Flow and Oxygen Consumption in Man. Physiol. Rev., 39:183, 1959.
18. Lewis, F. J. and Tauffic, M.: Closure of Atrial Septal Defects with the Aid of Hypothermia: Experimental Accomplishments and the Report of One Successful Case. Surgery, 33:52, 1953.

19. McCall, M. L., Taylor, H. W. and Finch, T. V.: The Effects of Intravenously Administered Sodium Amytal on Cerebral Circulation and Metabolism in Toxemia of Pregnancy. J. Phila. Gen. Hosp., 3:110, 1952.

20. Malette, W. G., Fitzgerald, J. B. and Eiseman, B.: Hypercapnia: A Means of Increasing Oxygen Availability During Hypothermic Perfusion. Surg. Forum, 12:184, 1961.

21. Michenfelder, J. D. and Theye, R. A.: Hypothermia: Effects on Canine Brain and Whole Body Metabolism. Anesthesiology, 29:1107, 1968.

22. Mohri, H., Barnes, R. W., Winterscheid, L. C., Dillard, D. H. and Merendino, K. A.: Challenge of Prolonged Suspended Animation: A Method of Surface-induced Deep Hypothermia. Ann. Surg., 168:779, 1968.

23. Mohri, H., Hessel, E. A., Nelson, R. J., Matano, I., Anderson, H. N., Dillard, D. H. and Merendino, K. A.: Use of Rheomacrodex and Hyperventilation in Prolonged Circulatory Arrest Under Deep Hypothermia Induced by Surface Cooling. Amer. J. Surg., 112:241, 1966.

24. Pevsner, P. H., Bhushan, C., Ottesen, O. W. and Walker, A. E.: Cerebral Blood Flow and Oxygen Consumption: An On-line Technique. Johns Hopkins Med. J., 128:134, 1971.

25. Rittenhouse, E. A., Mohri, H. and Merendino, K. A.: Circulatory Dynamics During Surface-induced Deep Hypothermia and After Cardiac Arrest for One Hour. J. Thorac. Cradiovasc. Surg., 61:359, 1971.

26. Rosomoff, H. L. and Holaday, D. A.: Cerebral Blood Flow and Cerebral Oxygen Consumption During Hypothermia. Am. J. Physiol., 179:85, 1954.

27. Schmidt, C. F., Kety, S. S. and Pennes, H. H.: Gaseous Metabolism of the Brain of the Monkey. Amer. J. Physiol., 143:33, 1945.

28. Swan, H., Virtue, R. W., Blount, S. G., Jr. and Kircher, L. T., Jr.: Hypothermia in Surgery, Analysis of 100 Clinical Cases. Ann Surg., 142:382, 1955.

Plasma Catecholamines in Patients with Serious Postoperative Infection

ALAN C. GROVES, M.D., F.R.C.S.(C), JOHN GRIFFITHS, M.D.,
F. LEUNG, PH.D., R. N. MEEK, M.D.

*From the Department of Surgery, Shaughnessy Hospital and
The University of British Columbia, Vancouver, B.C., and
The Department of Clinical Biochemistry,
University Hospital, University of Western Ontario,
London, Ontario*

PREVIOUS REPORTS indicate that urinary catecholamine excretion is not significantly increased in patients after major operation, but is elevated following severe trauma or during a complicated postoperative course. Measuring urinary catecholamines after major surgical procedures, Franksson, Gemzell and Euler[10] found that epinephrine was not elevated in patients who made an uneventful recovery. Although urinary excretion of norepinephrine was increased occasionally, it was normal in the majority of these patients. Patients with major trauma or postoperative complications had consistently increased urinary norepinephrine. In patients with burns Goodall, Stone and Haynes[12] found increased urinary excretion of catecholamines. The rise of norepinephrine was usually greater than epinephrine and was approximately proportional to the severity of the burns. Goodall[13] also observed histological depletion of catecholamine granules in the adrenal medulla of patients who died following severe burns. Urinary catecholamines do not reflect the intermittent circulating plasma concentrations, and in septic patients with or without hypotension, oliguria or anuria may preclude measurement of urinary catecholamines.

Using the ethylenediamine method, Hammond, Aronow and Moore[16] measured plasma catecholamines in a group of surgical patients. They found that plasma norepinephrine and epinephrine were normal in most patients following major surgical procedures, but were increased in patients with postoperative complications. The ethylenediamine method for the determination of plasma catecholamines has been criticized for its inability to distinguish accurately between norepinephrine and epinephrine;[21] hence a batch method using the more discriminating trihydroxyindole method to measure plasma norepinephrine and epinephrine has been developed in this laboratory.[14]

It has not been demonstrated previously that patients with sepsis following operation have plasma catecholamine concentrations greater than those seen in non-septic postoperative patients. This study reports the concentration of plasma norepinephrine and epinephrine measured in patients with severe septic complications following operation and a group of postoperative patients without infection.

Materials and Methods

Ten patients in an intensive care unit with life threatening forms of sepsis such as septicemia, gas gangrene and poorly controlled intra-abdominal abscesses formed the study group. Blood pressure, pulse, temperature, central venous pressure and urine output were recorded. Simultaneously, arterial blood was drawn for measurement of pH, P_{O_2} and P_{CO_2} on a Radiometer Model 27 blood gas analyzer, and venous blood was obtained for determination of plasma catecholamines.[14] Similar studies were made from a control group of ten non-septic patients on the first and second days after operation.

Submitted for publication March 17, 1972.

Reprint requests: Dr. John Griffiths, Chairman, Dept. of Clinical Biochemistry, University Hospital, University of Western Ontario, London, Ontario, Canada.

TABLE 1. *Postoperative Patients with Sepsis*

Patient	Day Observed	NE ng./ml.	E ng./ml.	Pulse	B. P. mm. Hg	CVP cm. H_2O	Urine ml./hr.	Temp. °C	pH	pCO_2 mm.Hg	Diagnosis
1 54 years	1	2.47	0.02	110	100/60	10	50	37.4	7.29	46	*Cl. welchii* cellulitis (R) flank, disseminated intravascular coagulation
	3	0.48	0.02	108	95/50	4	200	37.0	7.50	32	
	4	0.35	0.12	104	85/55	7	45	37.3	7.43	32	
	5	0.35	0.05	100	100/65	6	65	37.0	7.42	29	
2 31 years	1	2.33	0.25	160	110/70	7	200	38.0	7.51	32	*E.coli* abdominal abscesses post appendectomy
	2	2.19	0.25	160	110/70	0	30	38.4	7.48	27	
	3	1.05	0.14	135	120/70	0	50	38.7			
	6	0.84	0.23	132	130/95	3	75	37.5	7.41	42	
	7	1.12	0.39	140	125/80	3	40	37.8			
3 53 years	1	4.10	1.53	150	80/40	4	0	40.8	7.21	28	Esophagectomy for Ca esophagus, *Proteus morganii* septicemia
	1	3.91	1.03	144	70/30	6	0	41.0	7.19	24	
	1	3.80	0.94	130	80/50	7	15	40.0	7.20	23	
	1	2.87	1.12	140	70/40	7	24	40.0	7.23	27	
4 62 years	1	1.65	0.23	170	140/80		30	39.0			*Cl. welchii* cellulitis (R) flank
	2	1.08	0.28	124	160/80	16	45	38.8	7.35	38	
	4	0.43	0.08	100	160/80	9	100	38.8	7.45	43	
5 59 years	1	1.49	0.40	150	60/30	13	0	41.0	7.22	43	Anterior resection, Cl. welchii cellulitis and myositis abdominal wall, renal failure
6 27 years	1	2.26	0.33	120	150/80		0	36.7	7.29	47	*A. aerogenes* infection in compound fracture (R) leg, renal failure
	2	1.98	0.17	120	130/80	6	0	37.0	7.26	52	
	3	1.77	0.32	135	140/80	1	0	38.6	7.38	42	
	4	1.56	0.05	135	130/80	3	10	38.0			
	32	0.40	0.01	100	140/90		125	37.4			
7 83 years	1	3.16	0.48	130	100/60	8	15	39.0	7.28	23	Prostatectomy, *E. coli* septicemia
	1	2.49	0.39	124	95/50	9	25	39.2	7.29	31	
	1	2.36	0.51	128	90/50	7	65	41.0	7.30	27	
	1	1.65	0.36	110	100/60	6	70	38.0	7.31	36	
	2	1.42	0.32	104	110/60	7	110	38.2	7.38	29	
	2	0.75	0.14	96	110/60	7	250	37.0	7.39	34	
8 72 years	1	1.55	0.30	115	100/70	9	35	39.8	7.57	15	Post-op Longmire procedure, *Pseudomonas aeruginosa* septicemia
	3	0.29	0.03	70	90/55	5	80	37.0	7.49	28	
	4	0.64	0.02	76	100/60	7	50	36.3	7.46	33	
	5	0.42	0.15	80	90/60	4	45	36.5			
9 47 years	1	0.92	0.09	88	80/40	11	25	41.0	7.37	29	(R) Hemicolectomy, *E. coli* septicemia
	1	0.51	0.03	74	100/70	12	120	39.0	7.43	28	
	1	0.49	0.06	76	110/70	10	200	37.0	7.36	34	
	1	0.39	0.08	78	110/70	10	100	37.0	7.39	37	
10 32 years	1	1.81	0.13	110	140/70	6	90	39.0	7.45	30	Leaking duodenal stump post gastrectomy, peritonitis, *Klebsiella pneumoniae, Proteus morganii, Strep. fecalis*
	2	0.44	0.10	80	125/70	8	100	37.5	7.49	25	
	3	0.51	0.08	72	110/70	6	60	38.0			
	4	0.39	0.12	80	125/55	8	60	38.0			
	5	0.84	0.20	120	125/65	7	55	39.7	7.48	25	
	6	0.41	0.08	72	140/75	7	105	37.7			

Normal NE .25 ± .10 ng./ml
Normal E .04 ± .04 ng./ml

Results

Postoperative Patients with Sepsis (10), Table 1: When the seriously ill patients were first seen, mean plasma norepinephrine was 2.17 ng./ml. (± 0.92) and mean plasma epinephrine was 0.38 ng./ml. (± 0.43). Using the student *t* test on these data and the data obtained on the first postoperative day from the group without infection, it was found that plasma norepinephrine ($p < 0.001$) and plasma epinephrine ($p < 0.05$) were significantly greater in the septic patients. It was not possible to compare the second norepinephrine and epinephrine concentrations between the septic and non-septic patients since the intervals between collection of blood varied considerably in the septic group.

In every patient with sepsis, plasma norepinephrine was higher than plasma epinephrine. An analysis of co-

TABLE 2. *Postoperative Patients Without Sepsis*

Patient	Day post-op.	NE ng./ml.	E ng./ml	Pulse min.	B. P. mm. Hg	Urine ml./hr.	Temp. °C	Operation
1	First	0.54	0.32	100	190/75	75	36.9	Aorto-femoral bypass
	Second	0.57	0.46	110	190/75	125	37.5	
2	First	0.60	0.13	72	150/80	80	37.0	Splenectomy for idiopathic thrombocytopenic purpura
	Second	0.28	0.06	88	120/65	70	38.0	
3	First	0.30	0.06	84	165/80	75	37.2	Cholecystectomy and operative cholangiogram
	Second	0.17	0.05	80	180/90	50	37.0	
4	First	0.15	0.02	78	150/85	60	37.0	Cholecystectomy, common bile duct exploration, sphincterotomy
	Second	0.15	0.04	84	145/80	50	37.4	
5	First	0.38	0.01	120	110/70	55	36.4	Cholecystectomy
	Second	0.47	0.01	120	110/75	60	37.0	
6	First	0.29	0.24	94	150/80	50	37.0	Inguinal hernia repair
	Second	0.43	0.38	82	145/75	70	37.6	
7	First	0.18	0.04	68	130/90	45	36.8	Bilateral inguinal hernia repair
	Second	0.19	0.07	68	120/80	55	36.8	
8	First	0.44	0.05	104	140/80	80	37.6	Bilateral varicose vein, stripping and ligation
	Second	0.27	0.08	100	140/80	50	37.8	
9	First	0.15	0.02	68	150/60	60	36.8	Femoral popliteal bypass
	Second	0.18	0.07	80	150/80	40	37.3	
10	First	0.40	0.14	94	130/70	75	37.4	Femoral popliteal bypass
	Second	0.52	0.14	92	125/75	80	37.4	

Normal NE .25 ± .10 ng./ml.
Normal E .04 ± .04 ng./ml.

variance to compare the changes in both catecholamines showed a rise of norepinephrine correlated with a rise of epinephrine ($r = 0.77$, $p < 0.01$ at 95% confidence limits). Plasma catecholamines were elevated when either urinary output or central venous pressure indicated that volume replacement was not necessary. Seven of the ten patients with sepsis were not hypotensive when plasma norepinephrine and epinephrine were elevated, and although arterial P_{CO_2} was slightly increased on occasion, it was usually normal or low when the catecholamines were high. Six patients in this group died from the complications of sepsis.

Postoperative Patients without Sepsis (10), Table 2: Twenty-four hours after surgery, mean plasma norepinephrine was 0.34 ng./ml. (±0.16) and mean plasma epinephrine was 0.10 ng./ml. (±0.10). On the second postoperative day, mean plasma norepinephrine was 0.32 ng./ml. (±0.16) and mean plasma epinephrine was 0.14 ng./ml. (±0.15). The paired comparison *t* test did not show a significant change in mean plasma norepinephrine or epinephrine from the first to the second day. In some patients in this group, both catecholamines exceeded the normal range but mean plasma norepinephrine and epinephrine were within or near the upper limit of normal observed previously in healthy adults. Plasma norepinephrine always exceeded plasma epinephrine, but analysis of covariance at 95% confidence limits indicated that there was no correlation between these catecholamines. All patients in this group had an unremarkable postoperative course and none died.

Relationship of Plasma Catecholamines to Systolic Blood Pressure and Pulse: Fisher's 'Z' transformation technic was used to examine the relationship of plasma norepinephrine and epinephrine to systolic blood pressure and pulse in septic and nonseptic patients. In postoperative patients without infection, increased systolic blood pressure correlated with increased plasma epinephrine ($r = 0.65$, $p < 0.02$) but in the postoperative patients with serious septic complications, systolic blood pressure fell as plasma epinephrine increased ($r = -.47$, $p < 0.02$). There was no correlation of plasma norepinephrine with systolic blood pressure and pulse or plasma epinephrine with pulse in either group.

Case Reports

Case 1. This 54-year-old lady was admitted with central abdominal pain and a diagnosis of small bowel obstruction. Laparotomy was performed and small bowel adhesions lysed. During

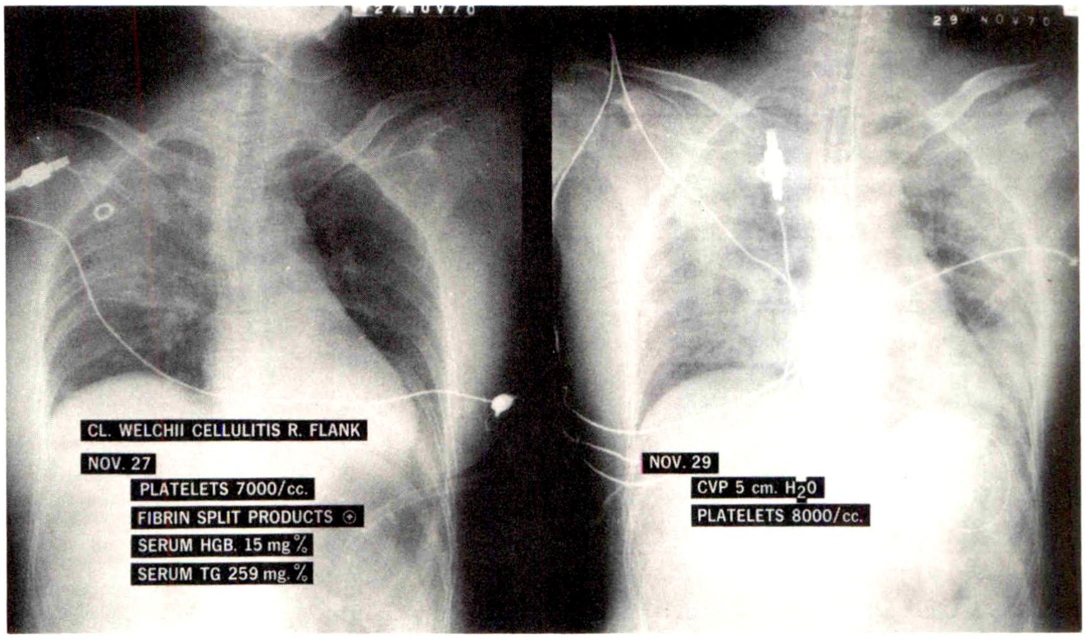


FIG. 1. This patient with *clostridium welchii* cellulitis of the right flank and disseminated intravascular coagulation had radiological evidence of pulmonary edema, but central venous pressure was normal.

operation the small bowel was inadvertently entered but closed without difficulty. Twenty-four hours following operation she became confused, her pulse was 140 per minute, temperature, 40°C, respiratory rate, 28 per minute and urine output, 10 ml. per hour. Crepitation originating in the abdominal wound and extending into the right flank was palpated and gram positive bacilli were identified on a gram stain of the wound exudate.

She was given massive doses of penicillin and taken to the hyperbaric chamber where debridement was performed during a 2-hour treatment with 100% oxygen at 3 ATA. The same evening she was given a second 2-hour hyperbaric oxygen treatment and her general condition improved. The next morning it was noted that the serum hemoglobin was 15 mg./100 ml., platelets, 7000/cc. and fibrin split products were present in the plasma. Plasma norepinephrine was 2.47 ng./ml., plasma epinephrine, 0.02 ng./ml., and serum triglyceride, 259 mg./100 ml. At this time blood pressure was 100/60, pulse, 110, central venous pressure, 10 cm. H_2O, urine output, 50 ml./hr. and P_{CO_2}, 46 mm.Hg. Two days later it was noted that she had lung lesions which occur in association with severe sepsis, that is, radiologic changes consistent with the diagnosis of pulmonary edema in association with a normal central venous pressure (Fig. 1). On the fifth day after the onset of the illness plasma norepinephrine and serum triglyceride had returned to normal, and 10 weeks later, after secondary wound closure and skin grafting, she was discharged from hospital.

Case 2. Six weeks previously, this 31-year-old patient had a ruptured appendix followed by three surgical procedures for drainage of abdominal and pelvic abscesses and a Bacteriodes organism was cultured from the purulent exudate. Despite this aggressive surgical treatment she continued to complain of severe abdominal pain, but on physical examination there was no localized abdominal tenderness. Six days later her condition had deteriorated considerably and there was generalized abdominal tenderness on palpation. Her pulse was 160 per minute, respiratory rate, 32 per minute, temperature, 38°C., central venous pressure, 7 cm. H_2O, urine output, 200 ml./hr., P_{O_2}, 86 mm.Hg, P_{CO_2}, 32 mm.Hg and pH, 7.51. She was confused and there was marked peripheral cyanosis. Plasma norepinephrine was 2.33 ng./ml. and plasma epinephrine, 0.25 ng./ml. The following day laparotomy was performed and three separate abdominal abscesses were drained. *Escherichia coli* bacteria were cultured from pus obtained at operation.

Immediately following operation her clinical condition was unchanged; plasma norepinephrine was 2.19 ng./ml. and plasma epinephrine, 0.25 ng./ml. On the second postoperative day her pulse had decreased to 135 per minute, there was no peripheral cyanosis and plasma norepinephrine and epinephrine had decreased to 1.05 ng./ml. and 0.14 ng./ml. respectively. By the fourth postoperative day she had improved further, and her plasma norepinephrine was 0.84 ng./ml. and plasma epinephrine, 0.23 ng./ml. She continued to improve and subsequently was discharged from the hospital.

Discussion

The data in this study show that plasma norepinephrine and epinephrine were slightly increased in some patients following uneventful major surgical procedures, but mean plasma norepinephrine and epinephrine were near the upper limit of normal observed in healthy adults. However, both norepinephrine and epinephrine were significantly higher in postoperative patients with severe septic complications than in postoperative patients without sepsis. While it is recognized that urinary catecholamine excretion is difficult to relate to plasma concentrations, these data are consistent with the observations of Franksson, Gemzell and Euler.[10] Increased systolic blood pressure was correlated with increased plasma epinephrine in postoperative patients without infection, but systolic blood pressure fell as plasma epinephrine increased in patients with serious septic complications. The physiological explanation for these results is unclear. Plasma norepinephrine always exceeded plasma epinephrine and occasionally remained elevated when epinephrine had returned to normal.

The cause of increased plasma catecholamines in patients with serious postoperative infection is not clear. Altered release, catabolism or excretion would affect plasma catecholamine concentrations, but the effect of sepsis on these parameters is unknown.

Long *et al.*[19] showed that in sepsis, glucose oxidation increased more than twice, whereas the metabolic rate increased only slightly. Muller, Faloona and Unger[24] have demonstrated that the plasma concentration of the gluconeogenic hormone, glucagon, increases when there is increased requirement for endogenous glucose. Since glucagon causes increased catecholamine release,[28] it is possible that additional glucose requirements in sepsis may raise plasma catecholamine concentrations indirectly. Duner's[8] studies indicate that a fall of blood glucose concentration initiates the release of catecholamines, particularly epinephrine, from the adrenal medulla via nervous pathways from the hypothalamus.[7] Direct stimulation of catecholamine release via the hypothalamus would be expected in dogs with hypoglycemia resulting from the intravenous injection of *E. coli* endotoxin,[2] and on occasion may occur clinically because hypoglycemia has been reported in patients with severe sepsis.[23]

Either metabolic or respiratory acidosis will raise plasma catecholamine concentrations.[20] Some of the patients in this study had metabolic acidosis which may have caused increased plasma catecholamines but none had significant respiratory acidosis. Hypotension will cause adrenal medullary catecholamine release via the baroreceptor reflex.[18] Although some patients in this study had low blood pressures, most were normotensive and none were hypovolemic when plasma catecholamines were elevated. These observations suggest that factors other than the baroreceptor reflex are more important causes of increased plasma catecholamines in postoperative patients with serious septic complications.

Gallin and associates[11] observed marked hyperlipidemia in association with lipid present in the prebeta fraction on lipoprotein electrophoresis of patients with serious gram-negative infection. In Case 1, transient hypertriglyceridemia associated with high plasma norepinephrine was observed. Fatty change also has been noted at postmortem in the liver of patients who died following gram-negative sepsis[25] and experimental infusion of norepinephrine into healthy dogs causes hypertriglyceridemia, increased very low density lipoprotein in the plasma[4] and acute fatty liver.[9] Recent studies in this laboratory showing a rise in serum triglyceride correlated with a rise in plasma norepinephrine but not epinephrine 12 hours after the injection of live *E. coli* bacteria into dogs suggest that the hypertriglyceridemia associated with gram-negative sepsis is related to endogenous norepinephrine release induced by gram-negative bacteremia.[15]

Both norepinephrine and epinephrine inhibit the insulin response to glucose.[26,27] Cerasi and colleagues[5] have shown by glucose and epinephrine infusion studies that inhibition of insulin release is dependent on the rate of infusion of epinephrine. However, at all rates of infusion which were studied, epinephrine reduced insulin secretion.[5] In patients with severe burns the negative nitrogen balance can be reduced greatly by infusions of glucose and insulin.[17] Since insulin is an anabolic hormone, the significance of impaired insulin release secondary to raised plasma catecholamines as a cause of the high catabolic rate in patients with serious postoperative infection requires further study.

Disseminated intravascular coagulation is a frequent complication of septicemia.[1] McKay[22] found hematological changes consistent with disseminated intravascular coagulation as well as electron microscopic evidence of fibrin in the microcirculation of rabbits and monkeys following continuous epinephrine infusion. Whitaker, McKay and Csavossy[29] also noted the severity of hemolysis and red cell fragmentation following epinephrine infusion was related to the amount of intravascular clotting. Both disseminated intravascular coagulation and hemolysis were completely prevented by prior alpha adrenergic blockade with dibenzyline but only partially prevented by heparin.

Berk[3] has suggested that increased beta rather than increased alpha adrenergic stimulation causes many of the pathophysiological changes in septic shock, and has reported encouraging results in the treatment of septic shock with the use of the beta adrenergic antagonist, propranolol. However, Carlson[4] noted a high mortality following a continuous 8-hour infusion of the alpha adrenergic drug, norepinephrine, into healthy dogs at the rate of 1 μg./Kg./min. A high mortality also has been reported in patients with severe sepsis, particularly if associated with hypotension,[6] and in this study in which norepinephrine concentration exceeded epinephrine concentration, there were six deaths in the group of ten patients with serious postoperative infection.

It is well recognized that norepinephrine or epinephrine are contraindicated in the treatment of patients with severe sepsis. It remains to be shown whether the increased plasma catecholamines noted in the postoperative septic patients are beneficial or detrimental. Experimental evidence suggests that sustained high concentrations of circulating catecholamines produce diverse deleterious effects; hence, further studies are needed to compare plasma catecholamine concentrations in animals subjected to continuous catecholamine infusion with those measured in patients with severe sepsis.

Summary

Plasma norepinephrine and epinephrine were slightly increased in some patients following uneventful major surgical procedures, but mean plasma norepinephrine and epinephrine were within or near the upper limit of normal observed in healthy adults. Both mean plasma norepinephrine and epinephrine were significantly higher in postoperative patients with severe septic complications than in postoperative patients without sepsis. Plasma norepinephrine always exceeded plasma epinephrine and occasionally remained elevated when epinephrine had returned to normal.

References

1. Attar, S., Hanashiro, P., Mansberger, A., McLaughlin, J., Firminger, H. and Cowley, R. A.: Intravascular Coagulation, Reality or Myth? Surgery, **68**:27, 1970.
2. Berk, J. L., Hagen, J. F., Beyer, W. H. and Gerber, M. J.: Hypoglycemia of Shock, Ann. Surg., **171**:400, 1970.
3. Berk, J. L., Hagen, J. F. and Dunn, J. M.: The Role of Beta Adrenergic Blockade in the Treatment of Septic Shock, Surg. Gynecol. Obstet., **130**:1025, 1970.
4. Carlson, L. A., Liljedahl, S. O., Wirsen, C.: Blood and Tissue Changes in the Dog During and After Excessive Free Fatty Acid Mobilization, Acta Med. Scand., **178**:81, 1965.
5. Cerasi, E., Luft, R. and Efendic, S.: Antagonism Between Glucose and Epinephrine Regarding Insulin Secretion, Acta Med. Scand., **190**:411, 1971.
6. Duff, J. H., Groves, A. C., McLean, A. P. H., Lapointe, R. and MacLean, L. D.: Defective Oxygen Consumption in Septic Shock, Surg. Gynecol. Obstet., **128**:1051, 1969.
7. Duner, H.: The Influence of Blood Glucose Level on Secretion of Adrenaline and Noradrenaline from the Suprarenal. Acta Physiol. Scand., **28**: Suppl. 102, 1953.
8. Duner, H.: Effect of Insulin Hypoglycemia on the Secretion of Adrenaline and Noradrenline from the Suprarenal of the Cat. Acta. Physiol, Scand., **32**:62, 1954.
9. Feigelson, E. B., Pfaff, W. W., Karmen, A. and Steinberg, D.: The Role of Plasma Free Fatty Acids in Development of Fatty Liver. J. Clin. Invest., **40**:2171, 1961.
10. Franksson, C., Gemzell, C. A. and von Euler, U. S.: Cortical and Medullary Adrenal Activity in Surgical and Allied Conditions, J. Clin. Endocrinol., **14**:608, 1954.
11. Gallin, J. I., Kaye, D., O'Leary, W. M.: Serum Lipids in Infection, N. Engl. J. M., **281**:1081, 1969.
12. Goodall, C. McC., Stone, C. and Haynes, B. W. Jr.: Urinary Output of Adrenaline and Noradrenaline in Severe Thermal Burns. Ann. Surg., **145**:479, 1957.
13. Goodall, C. McC.: Sympathoadrenal Medullary Response to Thermal Injury. J. Trauma, **7**:144, 1967.
14. Griffiths, J. C. and Leung, F. Y. T.: Fluorometric Determination of Plasma Catecholamines. Normal Human Epinephrine and Norepinephrine Values. Clin. Chim. Acta, **30**:395, 1970.
15. Griffiths, J. C., Groves, A. C. and Leung, F. Y. T.: Relationship of Plasma Catecholamines to Serum Triglyceride in Canine Gram-Negative Bacteremia, Surg. Gynecol. Obstet., **134**:795, 1972.
16. Hammond, W. G., Aronow, L. and Moore, F. D.: Studies in Surgical Endocrinology III, Plasma Concentrations of Epinephrine and Norepinephrine in Anaesthesia, Trauma and Surgery, as Measured by a Modification of the Method of Weil-Malherbe and Bone. Ann. Surg., **144**:715, 1956.
17. Hinton, P., Allison, S. P., Littlejohn, S. and Lloyd, J.: Insulin and Glucose to Reduce Catabolic Response to Injury in Burned Patients. Lancet, **1**:767, 1971.
18. Kaindl, F. and von Euler, U.S.: Liberation of Noradrenaline and Adrenaline from the Suprarenals of the Cat During Carotid Occlusion. Amer. J. Physiol., **166**:284, 1951.
19. Long, C. L., Spencer, J. L., Kinney, J. M., and Geiger, J. W.: Carbohydrate Metabolism in Man: Effect of Elective Operations and Major Injury. J. Appl. Physiol., **13**:110, 1971.
20. Malm, J. R., Manger, W. M., Sullivan, S. F. Papper, E. M., and Nahas, G. G.: The Effect of Acidosis on Sympathoadrenal Stimulation, JAMA, **197**:161, 1966.
21. Manger, W. M., Steinsland, O. S. Nahas, G. G., Wakim, K. G. and Dufton, S.: Comparison of Improved Fluorometric Methods Used to Quantitate Plasma Catecholamines. Clin. Chem., **15**:1101, 1969.
22. McKay, D. G., Whitaker, A. N., Cruse, V.: Studies in Catecholamine Shock, II. An Experimental Model of Microangiopathic Hemolysis. Amer. J. Pathol., **56**: 177, 1969.
23. Medalle, R., Webb, R. and Waterhouse, C.: Lactic Acidosis and Associated Hypoglycemia. Arch. Intern. Med., **128**:273, 1971.
24. Muller, W. A., Faloona, G. R. and Unger, R. H.: The Influence of the Antecedent Diet Upon Glucagon and Insulin Secretion. N. Engl. J. Med., **285**:1450, 1971.
25. Neely, W. A., Berry, D. W., Rushton, F. W. and Hardy, J. D.: Septic Shock: Clinical, Physiological and Pathological Survey of 244 Patients. Ann. Surg., **173**:657, 1971.
26. Porte, D., Williams, R. H.: Inhibition of Insulin Release by Norepinephrine in Man, Science, **152**:1248, 1966.
27. Porte, D., Graber, A. L., Kuzuya, T. and Williams, R. H.: The Effect of Epinephrine on Immunoreactive Insulin Levels in Man. J. Clin. Invest., **45**:228, 1966.
28. Scian, L. F., Westermann, C. D., Verdesca, A. S. and Hilton, J. G.: Adrenocortical and Medullary Effects of Glucagon. Amer. J. Physiol., **199**:867, 1960.
29. Whitaker, A. N., McKay, D. G., Csavossy, I.: Studies in Catecholamine Shock, I. Disseminated Intravascular Coagulation, Amer. J. Pathol., **56**:153, 1969.

Dipyridamode and Aspirin Tested Against an Experimental Model of Thrombosis

J. E. MAYER, JR., M.D.,* G. L. HAMMOND, M.D.

From the Surgical Cardiovascular Research Laboratory and the Department of Surgery, Yale University School of Medicine, New Haven, Connecticut

ARTERIAL RECONSTRUCTIVE surgery, especially in small vessels, may be complicated by early failure due to thrombosis.[14] Thrombosis after surgical or other injury to the arterial wall is initiated when the endothelium is destroyed and platelets adhere to subendothelial structures in the vessel wall such as collagen,[24] or basement membrane.[17] This initial thrombus formation may be unavoidable in vascular surgery as simple grasping of the vessel with a forceps can lead to disruption of the endothelium and adherence of platelets to the denuded areas.[2] The thrombus then grows as the initially adherent platelets release ADP,[20] serotonin,[20] and epinephrine,[22] to induce more platelets to aggregate. The initially adherent platelets also make platelet factor 3 available to activate the plasma coagulation system and generate thrombin and fibrin.[15] The activity of this platelet system, combined with the pattern of blood flow, ultimately determines whether the thrombus will grow to obstruct the lumen of the vessel.[21] The importance of platelet activity in determining the outcome of arterial reconstruction has been emphasized by Evans and Mustard who showed a correlation between platelet adhesiveness and the onset of occlusion in saphenous vein and dacron grafts.[12] Therefore, attempts to reduce the incidence of thrombosis complicating arterial reconstructive procedures can be directed at interrupting the initial platelet-mediated steps in arterial thrombus formation. The following studies were undertaken to evaluate the ability of two agents which affect platelet aggregation, dipyridamole and aspirin, to affect intra-arterial thrombosis.

Utilizing the proteolytic enzyme pronase to remove the intima and part of the muscularis layers of the vessel wall, a consistently clotting arterial model was devised against which dipyridamole and aspirin were tested.

Materials and Methods

Four groups of 25 Kg. adult mongrel dogs were anesthetized with intravenous barbiturates, intubated, and placed on a volume respirator. In Group I, consisting of 10 vessels in seven dogs, 4 cm. segments of femoral artery were isolated under sterile conditions, side branches were ligated, and #10 Bardic cannulas inserted into the proximal and distal ends of the isolate segment via two small longitudinal arteriotomies. Then, using a roller pump, a solution containing 0.25% pronase in normal saline was perfused through the segment at 200 cc./min. for 30 minutes. After perfusion, the vessels were flushed with normal saline to remove any residual pronase solution. All arteriotomies were closed with 6–0 everting sutures. In Group II, consisting of 6 vessels in four dogs, a similar procedure was followed except that the perfusate consisted of normal saline. In Group III, consisting of 10 vessels in five dogs, the procedure was the same as in Group I except that the dogs were given 250 mg. of dipridamole orally each day for 4 days before operation and this drug was then continued until the time of sacrifice. Group IV, consisting of 10 vessels in 5 dogs, was identical to Group II except that 40 grains (approximately 2.5 g.) of aspirin was given orally the day before operation and then continued each day until sacrifice. Patency of the vessels was determined *in vivo* by palpation of the pulse distal to the perfusion site, and at autopsy by direct examina-

---

Submitted for publication April 14, 1972.
Supported by Fannie E. Ripple Grant #215-9.

[*] Intern, Dept. of Surgery, University of Minnesota.

tion of the vessels. Microscopic sections were made of all vessels and stained with hematoxylin and eosin or Masson trichrome.

To determine the thrombogenicity of pronase, 4 drops of the 0.25% pronase solution were added to a tube of whole canine blood and to a standard citrated tube of canine blood. Lee White, prothrombin, and partial thromboplastin times were then determined by standard laboratory methods.

Results

In Group I, all 10 vessels perfused with pronase showed loss of the distal pulse within 3 hours after perfusion. Gross inspection of the vessels showed clot occluding the lumen, and microscopy showed that the intima and part of the musuclaris had been removed by the proteolytic action of the pronase. The thrombus occluding the lumen of the vessel was composed of a platelet mass, containing fibrin with trapping of red and white blood cells (Fig. 1), and was confined to the area perfused with the pronase solution.

In Group II, none of the 6 vessels perfused with saline clotted in 6 hours, at which time the dogs were sacrificed. There was no evidence of thrombus formation in the perfused area, and microscopy showed no disruption of the vessel wall (Fig 2).

In Group III, of the 10 vessels perfused, three clotted acutely, two were patent at sacrifice 6 hours postoperatively, and five were patent until sacrific at 2 to 6 weeks. In the vessels studied at 6 hours after perfusion, a thin layer of clot was present on the wall of the vessel on gross examination, but the lumen of the vessel was widely patent. The microscopic examination demonstrated this thin layer of platelets and fibrin on the vessel wall along with diffuse hemorrhage in the vessel wall (Fig. 3). In the vessels studied at 2 to 6 weeks after perfusion, no clot was noted grossly, and the luminal surface was covered with a smooth, shiny lining. On microscopic examination, no clot was seen, and the luminal surface of the vessel showed a fibroblastic proliferation by 2 weeks after the time of perfusion (Fig. 4). No unusual problems with hemostasis were noted in the animals receiving dipyridamole.

In Group IV, of 10 vessels, one clotted acutely and 9 remained patent at sacrific 6 hours to 6 weeks after perfusion. Gross findings at 6 hours consisted of a layer of clot in the area perfused but the vessels had remained patient. The findings at two weeks were similar to those in Group III with a fibroblastic proliferation in the damaged area covered with an endothelial-like layer of cells. Each of the animals in this group demonstrated a marked hemorrhagic tendency during operation which required the ligation of even the smallest bleeding points. In addition, there was a ten-

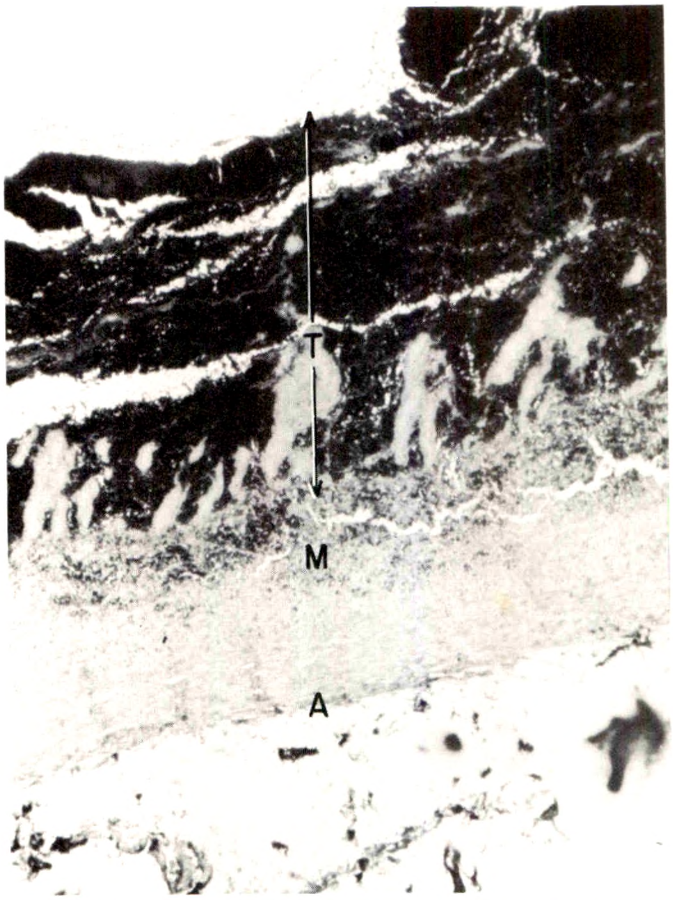


FIG. 1. Longitudinal section through one side of vessel wall (35×) showing thrombus (T) adherent to the media (M) after digestion of the intima and inner layers of media with pronase. (A) indicates the adventitial surface.

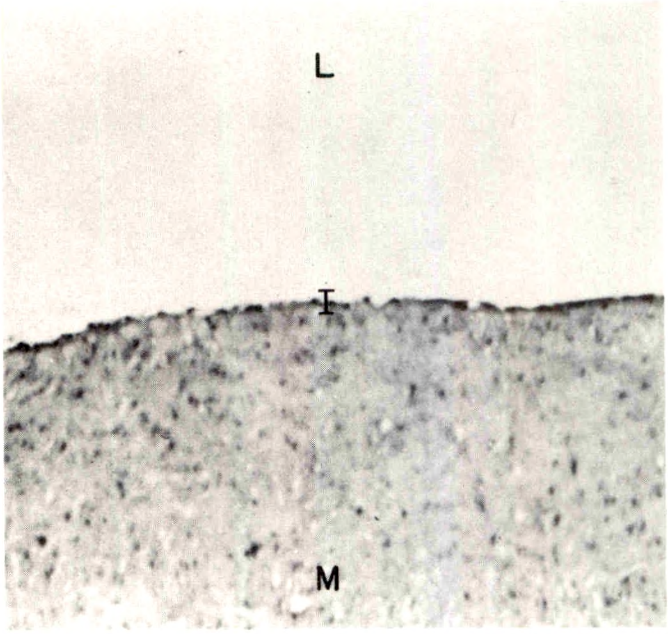


FIG. 2. Longitudinal section through one side of vessel wall (100×) after perfusion with saline. (I) indicates the intact intimal layer. (M) represents media. (L) is the lumen of the vessel.

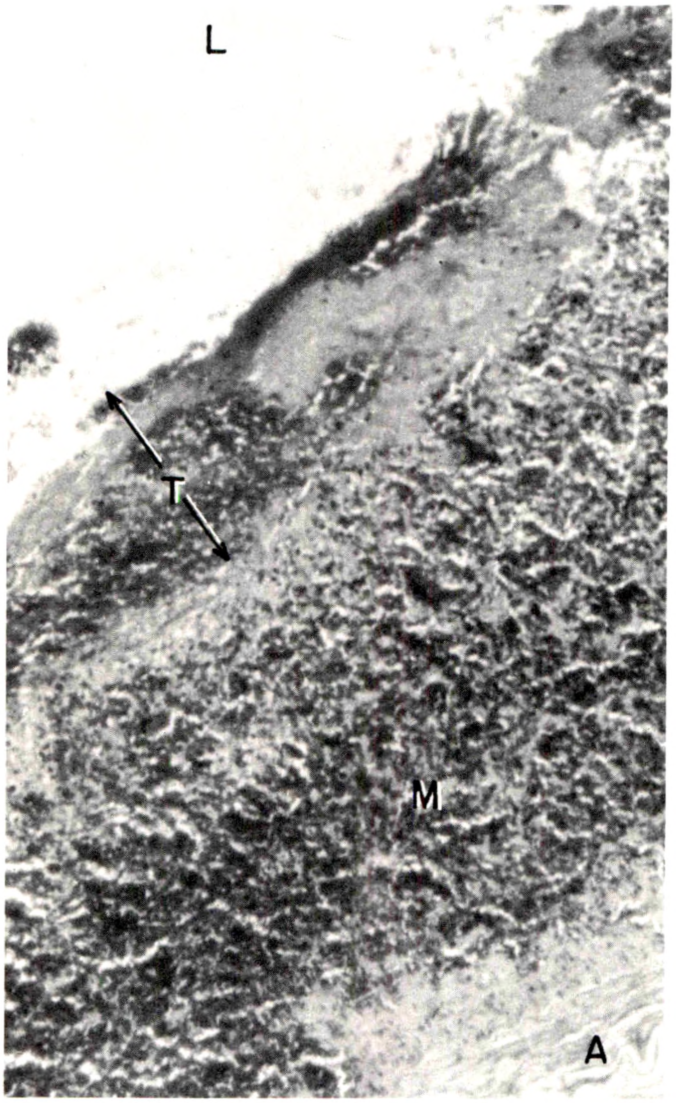


FIG. 3. Longitudinal section through one side of vessel wall (100×) from animal treated with dipyridamole 6 hours after perfusion with pronase. The amount of thrombus (T) is markedly reduced compared to that occurring after perfusion with pronase without prior administration of dipyridamole. (L) and (A) represent luminal and adventitial surfaces. There is hemorrhage into the medial layer (M) of the vessel wall.

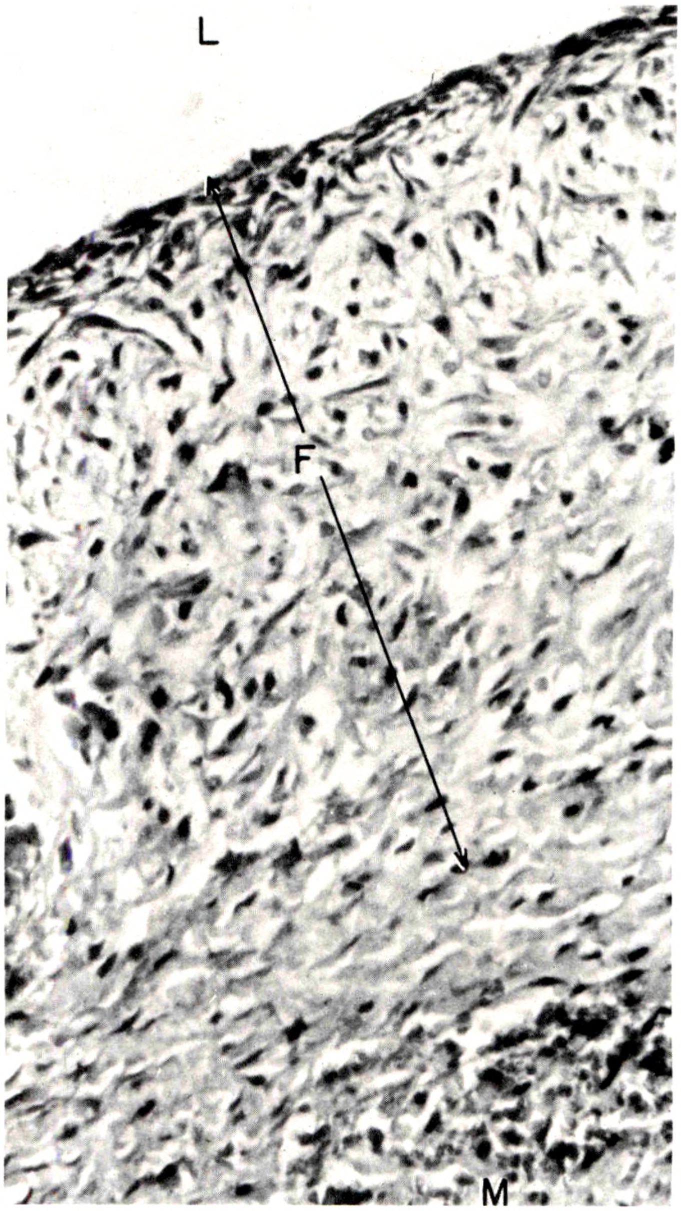


FIG. 4. Longitudinal section through one side of vessel wall (430) two weeks after perfusion with pronase in animal treated with dipyridamole. (F) refers to an area of fibroblastic proliferation on the luminal (L) surface of the vessel wall. (M) denotes media.

dency in this group of animals to develop hematomas in the operative site during the postoperative period.

Discussion

Perfusion of segments of artery with a 0.25% pronase solution has previously been shown to remove the intima and a variable amount of media depending on the length of perfusion.[18,23] These findings were confirmed by Group I of this series. After the restoration of normal blood flow, all vessels perfused with pronase developed thrombi which completely occluded the lumen of the vessel within 3 hours. In accordance with previously described observations of thrombosis following arterial injury,[19,21] microscopy showed platelets adherent to the damaged area of the vessel wall with formation of fibrin and trapping of red and white blood cells. The effect of pronase on the vessel wall is similar to that resulting from endarterectomy in the clinical setting in that the intima and part of the muscularis layers are removed. The 100% thrombosis rate after enzymatic endarterectomy is much higher than that resulting from mechanical endarterectomy in similar sized vessels clinically. However, as vessels perfused with saline did not thrombose, it was felt that the thrombosis in Group I did not result from technical error. Since pronase has been shown by Davey and Luscher to induce platelet aggregation *in vitro*,[8] it is possible that a small amount of pronase remaining on the vessel wall would have a direct effect on the blood to enhace thrombus formation. This effect was believed to be minimized by flushing the vessel with saline several times after the perfusion and before the restoration of blood flow. In addition, it should be noted that the concentration of pronase used by Davey to induce platelet aggreation was four times that in the initial perfusate in the present experiment. After flushing restoration of blood flow, the pronase would be diluted even further, so that it seems unlikely that the direct action of pronase on platelets was responsible for the the 100% thrombosis rate. The finding that the Lee White, prothrombin, and partial thromboplastin times were not altered by the addition of small amounts of the 0.25% pronase solution to samples of venous blood is some evidence that the thrombosis did not result from a direct effect of pronase on the blood. It would appear that the action of pronase induces some change in the vessel wall which makes it more thrombogenic than a vessel after simple mechanical endarterectomy. The ability of this model to produce thrombotic occlusion 100% of the time provided a valuable control against which anti-thrombotic agents could be evaluated.

Dipyridamole given at a dose of 250 mg./day to the animals in Group III appeared to play a role in preventing thrombotic occlusion in a significant percentage (70%) of the vessels perfused with pronase. The findings in this group correlate well with previous studies demonstrating the ability of dipyridamole to reduce thrombus formation *in vivo*.[5,6,9,11] In particular, Danese and Haimov have recently reported that 100 mg. of dipyridamole in 16 Kg. dogs would decrease the rate of occlusion 4 hours after endarterectomy.[6] However, Danese, Voleti and Weiss found that 200 mg. of dipyridamole per day did not decrease the rate of occlusion 2 days after endarterectomy or injury with sulfuric acid.[7] The reasons for the latter findings are unclear, but in neither of these studies was a 100% rate of thrombotic occlusion used as a control. The model using pronase in the present study was employed to provide this type of consistently clotting arterial mode. Significantly, dipyridamole did not inhibit thrombus formation completely as a layer of thrombus was demonstrated on the vessel wall 6 hours after restoration of blood flow. The effect seemed to be to reduce the growth of the thrombus and thus prevent occlusion of the lumen of the vessel. By 2 weeks after the time of perfusion the layer of thrombus found initially had completely resolved and had been replaced by a layer of fibroblastic proliferation.

Aspirin administration to the dogs in Group IV also provided significant protection against the development of thrombotic occlusion after perfusion with pronase. In the series reported by Danese and Haimov and Danese *et al.*,[7] aspirin reduced the incidence of occlusion after endarterectomy or chemical injury. The dose of aspirin employed in the present study, however, was much higher than that used in earlier studies, and may be responsible for the marked hemorrhagic tendency found. Aspirin, like dipyridamole, did not completely inhibit thrombus formation as a layer of clot was found along the vessel wall, but it did decrease the rate of complete occlusion.

The ability of dipyridamole and aspirin to reduce the incidence of thrombotic occlusion in this study likely results from their effects on platelets. *In vitro*, dipyridamole has been shown to inhibit the aggregation of platelets by ADP,[10] collagen,[5,22] and thrombin,[5,22] and inhibits the release of ADP,[5,22] and serotonin[5,22,27] from platelets after exposure to platelet aggregating agents. In man, dipyridamole has been shown to decrease the platelet turnover in patients with prosthetic heart valves.[16] The means by which dipyridamole affects platelet aggregation is not definitely known, but one or both of the following mechanisms may be involved. Adenosine has been shown to inhibit ADP mediated platelet aggregation,[3] and Bunag *et al.* found that dipyridamole could increase the level of adenosine in whole blood by retarding its entrance into red blood cells where it is normally degraded.[4] More recently, Cucuianu *et al.* found that dipyridamole could inhibit the uptake of adenosine, serotonin, and glucose by platelets *in vitro*, and postulated that these direct effects of dipyridamole on platelets were responsible for the inhibition of platelet aggregation.[5]

Aspirin has also been shown to affect platelet function decreasing platelet aggregation by connective tissue,[25] collagen,[13] thrombin,[13] and epinephrine.[26] Aspirin also inhibits the release of ADP and serotonin by aggregated platelets,[13] and decreases the amount of platelet factor 3 made available.[28] The mechanism by which aspirin inhibits platelet aggregation has been investigated by Al-Mondhiry *et al.*, and this group concluded that it results from acetylation of active sites on the platelet membrane.[1]

The ability of dipyridamole and aspirin to reduce the incidence of thrombotic occlusion after enzymatic removal of intima and muscularis, as shown in this study, may have clinical application in arterial surgery, especially in small vessels.

Summary

A consistently clotting arterial model was devised using the proteolytic enzyme pronase to remove the intima and muscularis layers of the vessel wall and

thereby induce thrombosis. The administration of dipyridamole or aspirin was found to decrease the rate of thrombotic occlusion after perfusion with pronase.

Acknowledgment

We would like to thank Mrs. Dorothy Farrell and Messers. Walter DeLuca, Spyros Condos, Mitchell Goins, and George Brenckle for technical assistance and Miss Cinda Baley for secretarial assistance.

References

1. Al-Mondhiry, H., Marcus, A. J. and Spaet, T. H.: On the Mechanism of Platelet Function Inhibition by Acetylsalicylic Acid. Proc. Soc. Exp. Biol. Med., **33**:632, 1970.
2. Ashford, T. P. and Freiman, D. G.: The Role of the Endothelium in the Initial Phase of Thrombosis. Am. J. Pathol., **50**:257, 1967.
3. Born, G. V. R.: Strong Inhibition by 2-Chloroadenosine of the Aggregation of Blood Platelets by Adenosine Diphisphate. Nature, **202**:95, 1964.
4. Bunag, R. D., Douglas, C. R., Imai, S. and Berne, R. M.: Influence of a Pyrimidopyrimidine Derivative on Deamination of Adenosine by Blood. Circ. Res., **15**:83, 1964.
5. Cucuianu, M. P., Nishizawa, E. E. and Mustard, J. F.: Effect of Pyrimido-Pyrimidine Compounds on Platelet Function. J. Clin. Lab. Med., **77**:158, 1971.
6. Danese, C. A. and Haimov, M.: Inhibition of Experimental Arterial Thrombosis in Dogs with Platelet Deaggregating Agents. Surgery, **70**:927, 1971.
7. Danese, C. A., Voleti, C. D. and Weiss, H. J.: Protection by Aspirin against Experimentally Induced Arterial Thrombosis in Dogs. Thromb. Diath. Haemorrh., **25**:288, 1971.
8. Davey, M. G. and Luscher, E. F.: Actions of Thrombin and Other Coagulant and Proteolytic Enzymes on Blood Platelets. Nature, **216**:857, 1967.
9. Didisheim, P.: Inhibition by Dipyridamole of Arterial Thrombosis in Rats. Thromb. Diath. Haemorrh., **20**:257, 1968.
10. Emmons, P. R., Harrison, M. J. R., Honour, A. J. and Mitchell, J. R. A.: Effect of Dipyridamole on Human Platelet Behavior. Lancet, **2**:603, 1965.
11. Emmons, P. R., Harrison, M. J. G., Honour, A. J. and Mitchell, J. R. A.: Effect of a Pyrimidopyrimidine Derivative on Thrombosis Formation in the Rabbit. Nature, **208**:255, 1965.
12. Evans, G. and Mustard, J. F.: Platelet Surface Reaction and Thrombosis. Surgery, **64**:273, 1968.
13. Evans, G., Packham, M. A., Nishizawa, E. E., Mustard, J. F. and Murphy, E. A.: The Effect of Acetylsalicylic Acid on Platelet Function. J. Exp. Med., **128**:877, 1968.
14. Garrett, H. E., Kotch, P. I., Green, M. T., Diethrich, E. B. and DeBakey, M. E.: Distal Tibial Artery Bypass with Autogenous Vein Grafts: An Analysis of 56 Cases. Surgery, **63**:90, 1968.
15. Hardisty, R. M. and Hutton, R. A.: Platelet Aggregation and the Availability of Platelet Factor 3. Br. J. Haematol., **12**:764, 1966.
16. Harker, L. A. and Slichter, S. J.: Studies of Platelet and Fibrinogen Kinetics in Patients with Prosthetic Heart Valves. N. Engl. J. Med., **283**:1302, 1970.
17. Hughes, J. and Mahieu, P.: Platelet Aggregation Induced by Basement Membrane. Thromb. Diath. Haemorrh., **24**:395, 1970.
18. Kabemba, J. M. and Hammond, G. L.: Chemical Degradation of the Intima from Normal Canine and Atherosclerotic Human Vessels. J. Surg. Res., **12**:313, 1972.
19. Marcus, A. J.: Platelet Function. N. Engl. J. Med., **280**:1213, 1969.
20. Mills, D. C. B., Robb, I. A. and Roberts, G. C. K.: The Release of Nucleotides, 5 Hydroxytryptamine, and Enzymes from Human Blood Platelets during Aggregation. J. Physiol, **195**:715, 1968.
21. Mustard, J. R., Jorgensen, L., Hovig, T., Glynn, M. F. and Rowsell, H. C.: Role of Platelets in Thrombosis in Pathogenesis and Treatment of Thromboembolic Diseases. Thromb. Diath. Haemorrh., Suppl., **21**:131, 1966.
22. Mustard, J. F. and Packham, M. A.: Factors Influencing Platelet Function: Adhesion, Release and Aggregation. Pharm. Rev., **22**:97, 1970.
23. Robertson, A. L. and Insul, W.: Dissection of Normal and Arteriosclerotic Human Artery with Proteolytic Enzymes in *Vitro*. Nature, **214**:5090, 1967.
24. Spaet, T. H. and Erichson, R. B.: The Vascular Wall in the Pathogenesis of Thrombosis. Thromb. Diath. Haemorrh. Suppl., **21**:67, 1966.
25. Weiss, H. H. and Aledort, L. M.: Impaired Platelet Connective Tissue Reaction in Man after Aspirin Ingestion. Lancet, **2**:495, 1967.
26. Weiss, H. J., Aledort, L. M. and Kochwa, S.: The Effect of Salicylates on the Hemostatic Properties of Platelets in Man. J. Clin. Invest., **47**:2169, 1968.
27. Zucker, M. B. and Peterson, J.: Effect of Acetysalicylic Acid, Other Non-Steroidal Anti-Inflammatory Agents, and Dipyridamole on Human Blood Platelets. J. Lab. Clin. Med., **76**:66, 1970.
28. Zucker, M. B. and Peterson, J.: Inhibition of Adenosine Diphosphate Induced Secondary Aggregation and Other Platelet Functions by Acetylsalicylic Acid Ingestion. Proc. Soc. Exp. Biol. Med., **127**:547, 1968.

Editorial

Thoughts Prompted by the Centennial of the American Public Health Association

ALLAN E. DUMONT, M.D.

A KIND of Olympian detachment characterizes the attitude of most surgeons in matters of public health. In 1874 Billroth expressed this view as follows: "The fanatical champions of public health are fighting for a goal that is too high for my myopic vision. I can admire the struggle but I cannot become involved in it."[1] While historical aspects of public health may seem even more remote to many of us, 1972 marked a milestone which should not go unnoticed by American surgeons. This is the 100th anniversary of the founding of The American Public Health Association. Of pivotal importance in the development of almost all progress in this field, the Association was founded largely through the efforts of a young, practicing surgeon, Dr. Stephen Smith of New York City. Smith served as the first president of the Association and subsequently held that office four times.

The story of Stephen Smith's involvement in the problems of community health is a fascinating adventure of the spirit. A brief excerpt from his remarks made at the celebration of the Association's 50th anniversary conveys the timeless quality of such an experience.[3]

"I came to New York from a small farm in the highlands of the state in 1850 for the purpose of completing my medical studies at the College of Physicians and Surgeons of Columbia University. I had selected medicine as my profession on the suggestion of my physicians as a preventive measure against the recurrence of a form of indigestion of which I had been a victim from childhood. To that advice I attribute my activities in middle life and the comparatively comfortable age to which I have attained.

Upon graduation, I joined the resident staff of Bellevue Hospital after a competitive examination, and after 2 years' residence in that great laboratory of disease of every kind and form, entered the field of private practice. During my term of service in Bellevue Hospital, a severe epidemic of typhus fever prevailed, due to an immense immigration of Irish people, among whom it first appeared following a famine. Ten of our staff of 12 suffered attacks, two of whom died. I was one of those who escaped. The pressure upon the accommodations of the hospital became so great that the commissioners established a fever hospital on Blackwell's Island, and I was appointed its visiting physician, being regarded as immune.

Upon examination of the records of admission of patients, I discovered that from one tenement house upwards of 100 cases had been received. On visiting the house, I found a veritable "fever nest." The doors and windows were broken, the cellar was filled with sewage, every room was occupied by families of Irish immigrants who had but little furniture and slept on straw scattered on the floor. I learned that the house was the first resort of immigrants, as there was no one in charge and hence no expense.

My first effort to vacate and close this fever nest was an application to the Police Department. During my interview with the president, the attorney of the board was called, and upon hearing the case informed us that the police had no authority to act in such cases, and he knew of no department of the city government that could legally take the steps which I proposed, namely to abate a nuisance of such a kind.

I then determined to find the owner and endeavor to persuade him as a matter of public duty and humanity to put his house in proper sanitary condition. Visiting the tax office, I found that the taxes were paid by a

From the Department of Surgery of New York University Medical Center, New York City 10016

Submitted for publication June 12, 1972.

wealthy gentleman living in Union Square. He received my request with a flat refusal to improve the house, alleging that it never paid anything and was a constant source of annoyance.

When I related the case, and my failures, to the secretary of the Citizens' Association, a powerful body of men, with Mr. Peter Cooper as president, organized to defeat the schemes of Tweed, then in full control of the city government, he was deeply interested and suggested that the reform of the Health Department was directly in line with the work of the Association. He suggested that I shouuld join the organization and become a member of the "Council of Hygiene," a committee already in operation and named after a French commission. I followed his advice, was elected and assigned to the Council, and became its secretary."

Smith's account goes on to describe how, with the help of William Cullen Bryant and the threat of publicity in New York's Evening Post, the landlord was "brought to terms." Accorrding to Smith's obituary in the *Transactions of the American Surgical Association* prepared by Dr. Charles N. Dowd (Smith died in 1922 at the age of 99) formation of New York City, State and National Boards of Health were direct outgrowths of this incident.[2] Smith later served as Commissioner of both the City and State Boards of Health and was appointed to the National Board by President Rutherford B. Hayes. In addition to these activities which also included a primary role in developing institutional care for the mentally ill, Smith continued work as a practicing surgeon at Bellevue, St. Vincents, Columbus and the City Hospitals. At the same time he remained an active teacher on the faculty of the Bellevue Hospital Medical College. He was particularly well known among surgeons of the day for his textbook, *The Principles and Practice of Operative Surgery* which appeared in three editions.

It appears that there is still plenty of room for the involvement of surgeons in matters of community health. Faced with questions concerning the wisdom of such an undertaking, surgeons may be reassured by recalling the origin of the American Public Health Association and the career of Stephen Smith.

References

1. Billroth, T.: The Medical Sciences in the German Universities. New York, Macmillan Company, p. 90, 1924.
2. Dowd, Charles N., Dr. Stephen Smith (Obituary): Trans. Am. Surg. Assoc., 41:XLVII, 1923.
3. Smith, S.: The History of Public Health 1871–1921. In A Half Century of Public Health. Mazyck, P. Ravenel, ed. New York, American Public Health Association, p. 1, 1921.

Letters to the Editor

Dear Dr. Rhoads: October 8, 1972

I should like to make a few comments about an article that appeared in the *Annals of Surgery* Vol. 176, July, 1972, page 49.

Doctors Fleming and Bowen have written a persuasive article comparing pressure-limited and volume-limited respirators. I am left with the impression that, in their opinion, volume limiting is superior to pressure limiting in chest injuries. I recognize that there has been a running argument as to the relative benefits of these two modalities, but I am of the opinion that the argument is irrelevant. The important factor involved is the skill and understanding of the operator and his ability to tailor the treatment to the patient.

First, I would like to criticize the selection of machines used in accumulating results and making comparisons. On one hand is the Emerson machine designed for intensive care and having a pressure capability of 65 cm. of water pressure. On the other hand, representing the pressure-limited group are two units designed primarily for IPPB and having pressure capabilities of 40 and 45 cm. of water. One of the more powerful pressure units designed for intensive care was certainly indicated.

I think it is axiomatic that the pressure-limiting valve on either type of machine must be set at a level which is, in the opinion of the operator, safe for the patient being treated. This is especially true of those machines which can be triggered by the patient. This being the case, I wonder why the volume-limited device was set at 65 cm. pressure whereas the pressure-limited units were confined to a range between 20 and 25 cm. then raised only to 40 cm. when the patient was allowed to get into trouble. I feel safe in saying that if the Emerson had been limited to 25 cm. and had been left there during the early phases of treatment, the course of the disease in both groups would have been similar, despite volume limitation.

It is quite obvious that neither machine delivers a constant volume of gas to the lungs in face of changing compliance and airway pressures. The volume-limited units, because of their mechanical design, partially compensate for decreasing compliance by an increased pressure. It is this increase in pressure rather than the limitation of delivered volume that expands (or maintains) lung capacity. If exhaled volumes are measured frequently (or constantly) as they should be, volume can be maintained just as readily with the pressure device as with the volume-limiting one. Exhaled volume must be monitored with the volume machine just as with the pressure machine because it is not able to compensate for leaks in the system. Relatively simple, inexpensive spirometers that are easily attached to the exhaust manifolds are available for continuous monitoring.

Compliance will decrease during the early stages of any significant lung injury as is demonstrated by the cases reported. Since the process is rapidly progressive and potentially fatal, it seems to me that blood gas determinations and exhaled volumes performed twice daily is grossly inadequate. Had observations been made frequently as is usually recommended, adjustments in the operation of both types of machine would have minimized complications in those patients on pressure units. Patients on the volume units would probably have done better.

In conclusion, I feel that constant monitoring of these patients is absolutely essential and either type of machine must be adjusted to compensate for rapidly-occurring changes in the patient's condition. I would prefer that the adjustments be made, or at least observed, by an intelligent and competent person rather than by a machine. Any machine which has a widely-adjustable flow rate, adequate pressure control and full range of oxygen/air mixtures can do the job in proper hands.

We cannot walk into a respiratory I.C.U., write a series of fixed orders then get involved in other matters and recheck 12 hours later. In those un-monitored hours, the lungs have been very busy accumulating fluid and getting stiff. Regaining lost ground is extremely difficult if not impossible.

Sincerely yours,
P. W. Ford, M.D.
931 Larch Drive
Bend, Oregon 97701

Dear Dr. Rhoads: January 12, 1973

Dr. Ford has raised some interesting points regarding our paper, and his comments point out the need for the following clarifications:

There is, of course, no way to substitute a machine for skill or knowledge on the part of the physician. An optimal machine may, however, free the physician from certain routine things.

The machines used in this study were those available to us, rather than those selected by us. However, these units are numerically quite representative of the machines in use in the United States today. Therefore, the choice involved is typical of that faced by most physicians.

Dr. Ford is correct that the compliance of the lungs being ventilated is important. This was pointed out by Peters in 1967, and re-emphasized by us in the discussion and bibliography of our article. The volume-limited machines all have the capability of maintaining an adequate tidal volume despite the variations in compliance characteristic of acute respiratory failure. Furthermore, the compensation for a falling compliance is largely made automatically by the volume-limited machine, and made immediately apparent by a rise in the peak pressure shown on a dial easily read by nurses and paramedical personnel. By constantly monitoring tidal volume and adjusting peak inspiratory pressure, the pressure-limited machine can be made to deliver consistently adequate tidal volume. However, the use of the pressure-limited machine in this way essentially converts it to a constant-volume respirator, but requires constant measuring and frequent adjusting which the volume-limited machine does instantly and automatically.

Regarding the frequency of measurements of pressure, blood gases, etc., we do not mean to imply that twice a day is adequate. Each patient must be followed individually, and virtually all of our patients were checked much more frequently. But for purposes of this protocol, the more accurate measurements for research purposes were made at least twice a day.

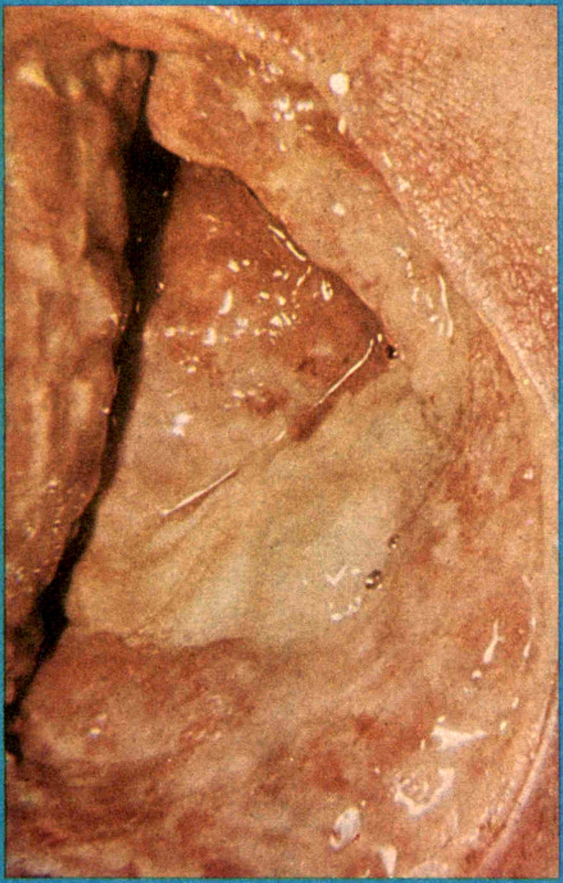
Given the instrumentation on the machines commonly in use today, we would still contend that patients will get better care with the volume-limited machines, where falling compliance will be recognized in seconds or minutes; and where at least partial compensation for this fall in compliance is automatically and instantaneously made. These machines will not free the physician from his responsibilities; but they will enable him to give better care to more patients during the same length of time.

Yours very truly,
William H. Fleming, M.D.
John C. Bowen, M.D.

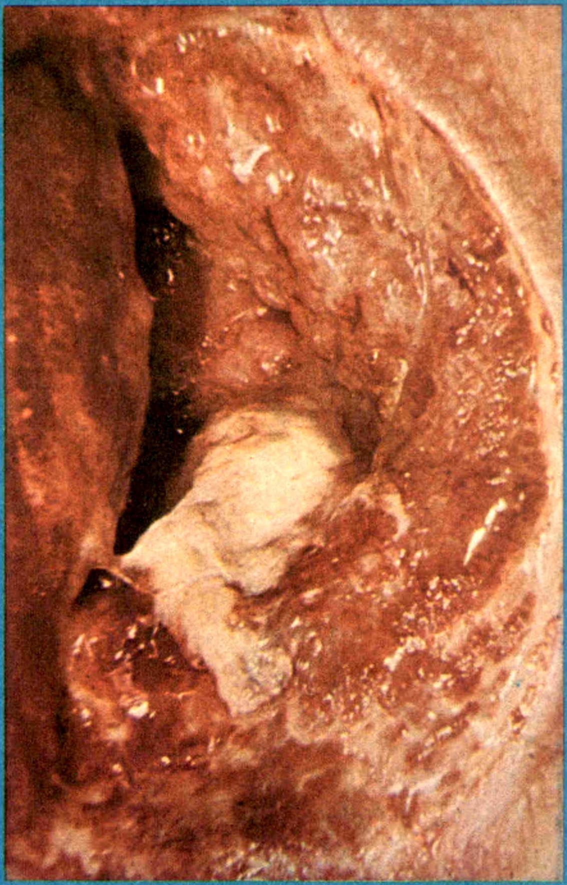
Decubitus Ulcers Yield to

Travase® Ointment

brand of **Sutilains**



Before treatment, necrotic matter coated the inner surfaces of this decubitus ulcer.



After six days of TRAVASE therapy, debridement is nearly complete and granulation evident.

djunctive Therapy—Observe Its Effects in 48 hours
Vhen the recommended nursing technique is ollowed without deviation, this procedure can enerate visible improvement within 48 hours of reatment. If no dissolution of slough occurs by then, urther application is unlikely to be rewarding recheck for break in procedure, usually due to use f cleansing or antiseptic agents which impair the ffectiveness of the enzyme in TRAVASE).

linical observation and photos by Kathleen Brough ldham, M.D., Marion County Home, Indianapolis, Ind.

lease see next page for prescribing information

First Class
Permit No. 39
Deerfield, Ill.

BUSINESS REPLY MAIL No Postage Stamp Necessary If Mailed in the United States

Postage Will Be Paid by Addressee

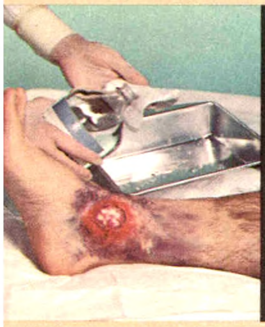
Flint Laboratories
Division of Travenol Laboratories, Inc.
200 Wilmot Road
Deerfield, Illinois 60015

Travase® Ointment brand of Sutilains

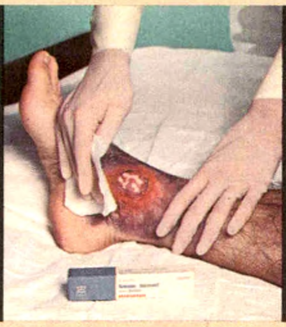
APPLICATION TECHNIQUE: TRAVASE Ointment is indicated as an adjunct to established methods of wound care for biochemical debridement. It dissolves and facilitates the removal of necrotic tissues and purulent exudates.

TRAVASE enzymes are selective. Virtually inactive on viable tissue.

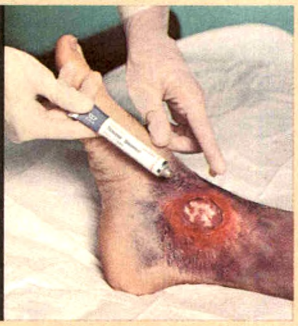
When this recommended nursing technique is followed without deviation, this procedure can generate visible improvement within 48 hours . . .



(Ulcer being irrigated) Thoroughly cleanse and irrigate the wound area using **only** sterile water or sodium chloride solution. Be sure to cleanse the wound of any antiseptics or heavy-metal antibacterial agents which may interfere with the enzyme activity.

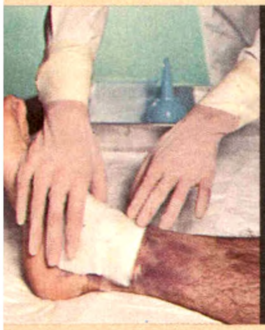


Thoroughly soak the wound area. Where practical, tubbing or showering is suitable. Or wet soaks with gauze pads may be used. Remember to avoid chemical cleansing agents which may interfere with the therapy.

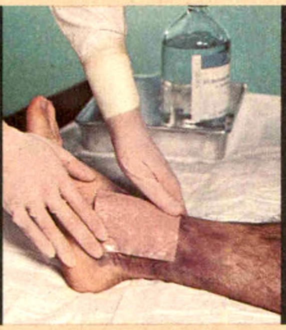


With a sterile cotton swab or finger cot, apply a very **thin** layer of TRAVASE Ointment. The ointment spreads easily and only a small amount is needed (a small dab of ointment will cover an area as big as the back of a hand).

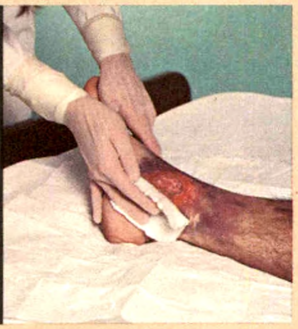
Be sure, though, to rub the ointment well into every crack or crevice of the wound and overlap the surrounding skin one-fourth to one-half inch beyond the area to be debrided—to be sure of complete coverage.



Apply loose, wet dressings, thoroughly soaked in sodium chloride solution or sterile water to the area to be debrided only.



Cover the moist dressings with an occlusive wrap (Saran wrap, Telfa Pads, or other plastic wrappings) to keep wound site moist. Do not extend occlusive wrap over ½ inch beyond area to be debrided.



When changing dressing, gently wipe away the dissolved material. Repeat the complete dressing procedure, including application of TRAVASE Ointment, four times daily.

The ulcer shown in these photos is simulated on a model in order to demonstrate the correct TRAVASE application technique.

To: FLINT LABORATORIES
Division of Travenol Laboratories, Inc.
200 Wilmot Road
Deerfield, Illinois 60015

Name ____________________

Title ____________________

Institution ____________________

Street ____________________

City ____________ State ____________ Zip ____________

Please send:

______Additional Information on TRAVASE® Ointment (brand of Sutilains)

______In-service training program

______Comment ____________________

DESCRIPTION: TRAVASE® (brand of sutilains) Ointment is a sterile preparation of proteolytic enzymes, elaborated by **Bacillus subtilis,** in hydrophobic ointment base consisting of 95% white petrolatum and 5 polyethylene. One gram of ointment contains approximately 82,000 cas units* of proteolytic activity.

ACTION: TRAVASE Ointment selectively digests necrotic soft tissues b proteolytic action. It dissolves and facilitates the removal of necrotic tissues and purulent exudates that otherwise impair formation of granulation tissue and delay wound healing (4).

At body temperatures these proteolytic enzymes have optimal activity i the pH range from 6.0 to 6.8.

INDICATIONS: For wound debridement (1,2)—TRAVASE Ointment is indicated as an adjunct to established methods of wound care for biochemical debridement of the following lesions:

Second and third degree burns,
Decubitus ulcers,
Incisional, traumatic, and pyogenic wounds,
Ulcers secondary to peripheral vascular disease.

CONTRAINDICATIONS: Application of TRAVASE (brand of sutilains) Ointment is contraindicated in the following conditions:

Wounds communicating with major body cavities,

Wounds containing exposed major nerves or nervous tissue,

Fungating neoplastic ulcers,

Wounds in women of child-bearing potential—because of lack of laboratory evidence of effects of TRAVASE upon the developing fe

WARNING: Do not permit TRAVASE Ointment to come into contact wit the eyes. In treatment of burns or lesions about the head or neck, sho the ointment inadvertently come into contact with the eyes, the eyes s be immediately rinsed with copious amounts of water, preferably steril

PRECAUTIONS: A moist environment is essential to optimal activity of enzyme. Enzyme activity may also be impaired by certain agents. **In vi** several detergents and antiseptics (benzalkonium chloride, hexachlorophene, iodine, and nitrofurazone) may render the substrate indifferent to the action of the enzyme (3). Compounds such as thimer containing metallic ions interfere directly with enzyme activity to a slight degree, whereas neomycin, sulfamylon-streptomycin, and penicil do not affect enzyme activity. In cases where adjunctive topical therap has been used and no dissolution of slough occurs after treatment wit TRAVASE Ointment for 24 to 48 hours, further application, because of interference by the adjunctive agents, is unlikely to be rewarding.

In cases where there is existent or threatening invasive infection, appropriate systemic antibiotic therapy should be instituted concurren

Although there have been no reports of systemic allergic reaction in humans, studies have shown that there may be an antibody response i humans to absorbed enzyme material.

ADVERSE REACTIONS: Adverse reactions consist of mild, transient pa paresthesias, bleeding and transient dermatitis. Pain usually can be controlled by administration of mild analgesics. Side effects severe enough to warrant discontinuation of therapy occasionally have occurr

If bleeding or dermatitis occurs as a result of the application of TRAV (brand of sutilains) Ointment, therapy should be discontinued. No syst toxicity has been observed as a result of the topical application of TRAVASE Ointment.

Dosage and Administration

STRICT ADHERENCE TO THE FOLLOWING IS REQUIRED FOR EFFEC RESULTS OF TREATMENT

1. Thoroughly Cleanse and Irrigate Wound Area with sodium chl or water solutions. Wound **MUST** be cleansed of antiseptics o heavy-metal antibacterials which may denature enzyme or alte substrate characteristics (e.g., Hexachlorophene, Silver Nitrat Benzalkonium Chloride, Nitrofurazone, etc.).
2. Thoroughly moisten wound area either through tubbing, show or wet soaks (e.g., sodium chloride or water solutions).
3. Apply TRAVASE Ointment in a thin layer assuring intimate co with necrotic tissue and complete wound coverage extending ¼ to ½ inch beyond the area to be debrided.
4. Apply loose wet dressings.
5. Repeat entire procedure 3 to 4 times per day for best results.

How Supplied

3P3002 TRAVASE Ointment is supplied sterile in one-half ounce tub (14.2 g.) containing 82,000 casein units of sutilains per gram hydrophobic ointment base.

The ointment must be stored under refrigeration at 2° to 10° C (35° to 50° F).

References

1. Garrett, T. A. **Bacillus subtilis** protease, a new agent for debrideme Clin. Med. **76:** 11-15, 1969.

2. Hesterberg, R. (Necrosis treatment on fermentative basis). Doctoral dissertation from the Chirurgical Clinic of the University of Munich. Dissertation Printing: Charlotte Schoen, Munich, 1964. (Ger.)

3. Howes, E. L. The healing of the burn may be hindered by its first a therapy. 20th Cong. Soc. Inter. Chir., Rome, Italy, September 14-23, 19

4. Prytz, B., Connell, J. F., Jr., and Rousselot, L. M. **Bacillus subtilis** protease in the digestion of burn eschar. Clin. Pharmacol. Therap. **7:** 347-51, 1966.

---

*A casein unit is the amount of enzyme required to produce the same optical density at 275 mμ as that of a solution of 1.5 mcg. tyrosine/m after the enzyme has been incubated with 35 mg. of casein at 37° C. one minute.

FLINT LABORATORIE
DIVISION OF TRAVENOL LABORATORIES, INC.
Morton Grove, Illinois 60053

serious enough for
Furacin® (nitrofurazone)

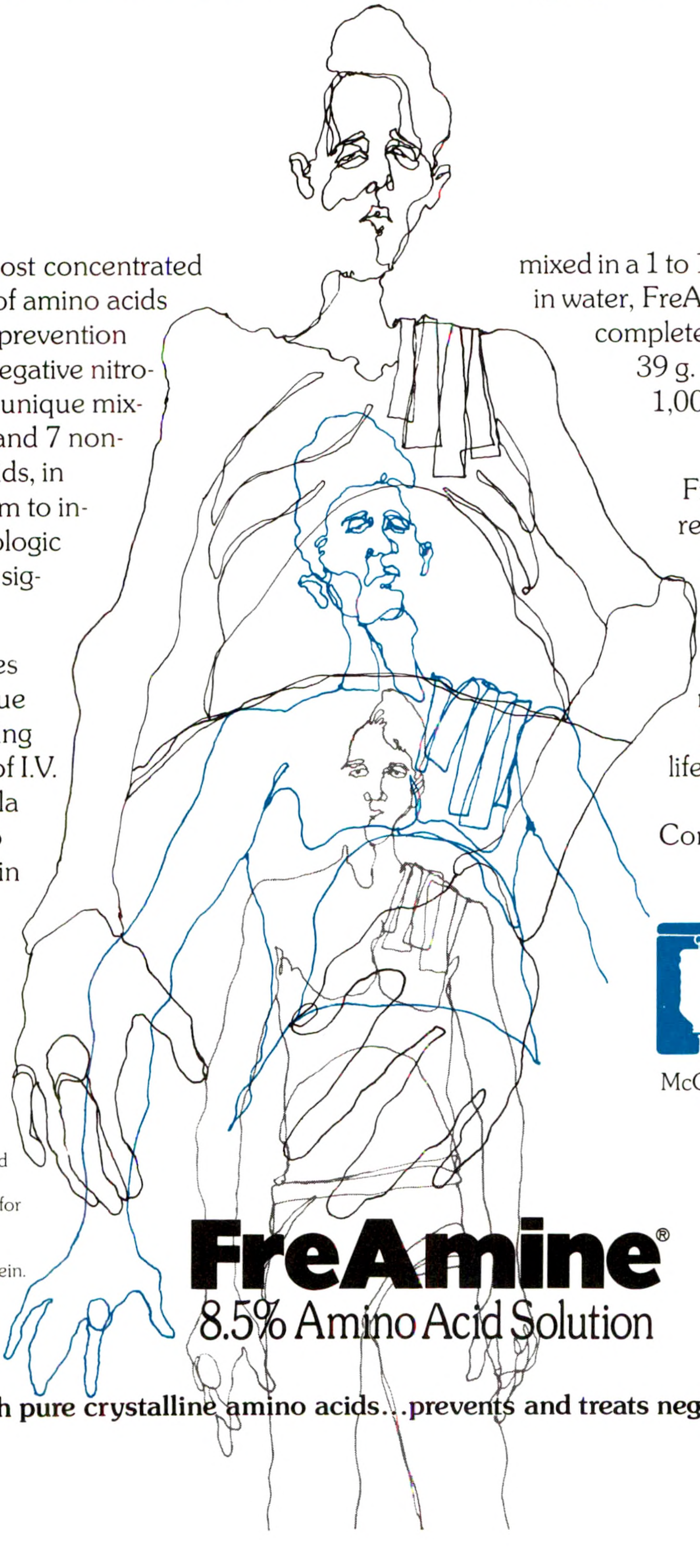
Furacin destroys most surface bacteria, yet is gentle to tissues—an important consideration when preparing burn wounds for skin grafting. Its action is not affected by blood, pus, or exudates, and development of resistant strains is unlikely. Furacin seldom sensitizes.

Indications: Adjunctive therapy for 2nd and 3rd degree burns when bacterial resistance to other agents is a real or potential problem. Skin grafting where bacterial contamination may cause graft rejection and/or donor site infections. **Contraindications:** Known prior sensitization to nitrofurazone. **Warnings:** Nitrofurazone has been shown to produce mammary tumors when fed at high doses to female Sprague-Dawley rats. The relevance of this to topical use in humans is unknown. *Safe use of nitrofurazone during pregnancy* has not been established. Use in women of child-bearing age is not recommended unless the therapeutic benefit outweighs the possible risk. **Precautions:** As with other topical antimicrobial agents, overgrowth of resistant organisms may occur. If this occurs, or if irritation, sensitization or superinfection develop, treatment with nitrofurazone should be discontinued and appropriate therapy instituted. **Adverse Reactions:** Furacin has not been significantly toxic in man by topical application. Sensitivity is low, with an overall incidence of 1.1 percent. Sensitivity reactions should be handled in a normal manner, except in the rare instance of severe contact dermatitis, when steroid administration may be indicated.

re-dress with Furacin

® Originators and Developers of The Nitrofurans
EATON LABORATORIES
Division of Morton-Norwich Products, Inc.
NORWICH, NEW YORK 13815

When life hangs on protein intake... FreAmine® is life-supportive.*



FreAmine is the most concentrated parenteral source of amino acids obtainable for the prevention and treatment of negative nitrogen balance. It is a unique mixture of 8 essential and 7 nonessential amino acids, in pure crystalline form to insure immediate biologic availability without significant waste.

FreAmine promotes anabolism and tissue synthesis even during extended periods of I.V. nutrition. Its formula is based on the two international protein standards. When mixed in a 1 to 1 ratio with 50% dextrose in water, FreAmine provides 6.25 g. of completely utilizable nitrogen and 39 g. of protein equivalent per 1,000 ml, plus 850 total nonprotein calories.

FreAmine is furnished in a ready-to-mix kit containing everything necessary for basic hyperalimentation, including 50% dextrose in water. Find out more about how McGaw puts it all together—with life-supporting I.V. nutrition in convenient kit form. Contact your McGaw representative or write for free brochure.

McGaw puts it all together.

*With adequate calories and other nutrients, when oral alimentation is not feasible for prolonged periods and/or there is impaired gastrointestinal absorption of protein.

FreAmine®
8.5% Amino Acid Solution

Supports life with pure crystalline amino acids...prevents and treats negative nitrogen balance.*

DESCRIPTION: Each 100 ml. contains: FreAmine Amino Acid Mixture*, 8.5 g; Sodium Bisulfite, U.S.P., less than 0.10 g.; Water for Injection, U.S.P. q.s., pH adjusted with acetic acid (approximately 20 mEq./1. Acetate).

Approximate concentration of amino acids (g./100 ml.):

Essential Amino Acids: L-Isoleucine 0.59; L-Leucine 0.77; L-Lysine HCl 0.77; Methionine 0.45; L-Phenylalanine 0.48; L-Threonine 0.34; L-Tryptophan 0.13; L-Valine 0.56.

Nonessential Amino Acids: L-Alanine 0.60; L-Arginine 0.31; L-Histidine 0.24; L-Proline 0.95; L-Serine 0.50; Aminoacetic Acid (Glycine) 1.8; L-Cysteine • HCl • $H_2O < 0.02$. Alpha amino nitrogen greater than 80% of total nitrogen present. Concentration of Electrolytes (mEq./1.): Sodium 10, Chloride 45.

8.5% FreAmine Solution is a sterile, nonpyrogenic solution containing pure crystalline amino acids. A 500 ml. unit provides a total of 39 g. of protein equivalent and 6.25 g. of nitrogen.

ACTIONS: 8.5% FreAmine Solution provides, in concentrated form, a physiological ratio of completely utilizable amino acids for protein synthesis. Used with concentrated carbohydrate solutions, e.g., 20 to 50% dextrose solutions, as a source of calories plus electrolytes and vitamins, it provides total parenteral nutrition.

INDICATIONS: As an adjunct in the prevention of nitrogen loss, or in the treatment of negative nitrogen balance in patients where: (1) oral alimentation is not feasible for prolonged periods, and (2) there is impaired gastrointestinal absorption of protein.

CONTRAINDICATIONS: 1. Anuria. 2. Hepatic coma.

WARNINGS: Administration of amino acids to a patient with hepatic or renal insufficiency may result in a rise in blood ammonia or urea nitrogen. Rare instances of typically asymptomatic hyperammonemia have been reported in patients with no evidence of liver dysfunction receiving total parenteral nutrition. Since it appears dose-related, and more likely to develop in infants on prolonged total parenteral nutrition, conservative doses of amino acids should be given and blood ammonia periodically measured. If symptomatic hyperammonemia should develop, the nitrogen-containing solution should be discontinued and the patient's clinical status reevaluated.

The safe use of FreAmine in pregnant women has not been demonstrated.

PRECAUTIONS: It is essential to provide adequate calories for utilization of amino acids.

Hypertonic nutrient solutions should be administered through an indwelling intravenous catheter with the tip located in the superior vena cava.

HYPERALIMENTATION COMPLICATIONS: Potentially dangerous complications can be minimized by adherence to a careful protocol by an experienced team of pharmacist, nurse, and physician.

To prevent sepsis, rigid aseptic technique must be used in solution preparation and catheter placement and care.

The catheter dressing should be aseptically changed every 2-4 days and whenever contamination is suspected.

Consult clinical literature for discussion of management of sepsis during hyperalimentation.

The following metabolic complications have been reported: metabolic acidosis, hypophosphatemia, alkalosis, hyperglycemia and glycosuria, osmotic diuresis and dehydration, rebound hypoglycemia, elevated liver enzymes, and electrolyte imbalances. Frequent clinical evaluation and laboratory determinations are necessary to prevent or minimize these complications.

ADVERSE REACTIONS: Rare instances of hyperammonemia (see Warnings), and minor local reactions consisting of a warm sensation and erythema when FreAmine and hypertonic dextrose were administered by peripheral vein, have been reported.

DOSAGE AND ADMINISTRATION: Recommended Dietary Allowances of protein are approximately 0.9 g. per kilogram of body weight for a healthy adult and 1.4 to 2.2 g. per kilogram for healthy growing infants and children.** Requirements in trauma or malnutrition may be substantially increased. During hyperalimentation daily doses of approximately 1.0 to 1.5 g. per kilogram of body weight for adults and 2 to 3 g. per kilogram of body weight for infants are generally sufficient.

Calorie-to-nitrogen ratios of at least 100 to 150 nonprotein calories per gram of nitrogen have been recommended and may be provided by concentrated dextrose.

Sufficient vitamins, electrolytes, principally potassium, magnesium, and phosphate, as well as sodium, calcium, and chloride, must be given. Calcium and phosphate may be added to alternate infusate bottles to avoid precipitation, and sodium and potassium added as acetate or lactate salts to provide bicarbonate precursor. Serum electrolytes must be monitored frequently.

In adults, hypertonic mixtures may be safely administered only by continuous infusion through a central venous catheter with the tip located in the vena cava. 500 ml. of 8.5% FreAmine Solution, appropriately mixed with dextrose, electrolytes, and vitamins, is typically administered over an eight-hour period. Administration rate is governed by protein requirements and glucose tolerance. Advance dosage slowly with frequent determination of urine and blood sugar levels.

To prevent rebound hypoglycemia, 5% dextrose should be administered when hypertonic dextrose infusions are abruptly discontinued.

PEDIATRIC DOSAGE AND ADMINISTRATION: Small infants (up to 10 kg.) on total parenteral nutrition generally receive 2 to 3 g. of protein, 100 calories, and 120 to 150 ml. of fluid per kg. of body weight per day, provided in a solution of approximately 2⅛% FreAmine in 20% dextrose. Advance dosage slowly with frequent monitoring. (See Warnings above)

Large infants and children generally require 50 to 80 calories per kg. per day.

ROUTE: Intravenous.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

HOW SUPPLIED: 8.5% FreAmine Solution is supplied sterile and nonpyrogenic in 500 ml. intravenous infusion bottles.

*Crystalline amino acid mixture, isolated and purified from edible soybean hydrolysate or synthesized.

**500 ml. of 8.5% FreAmine Solution contains 6.25 g. of nitrogen, and the equivalent of 39 g. of protein.

McGAW LABORATORIES
Division of American Hospital Supply Corporation
Glendale, California • Milledgeville, Georgia

THE QUICK-CHANGE ANOPERINEAL DRESSING

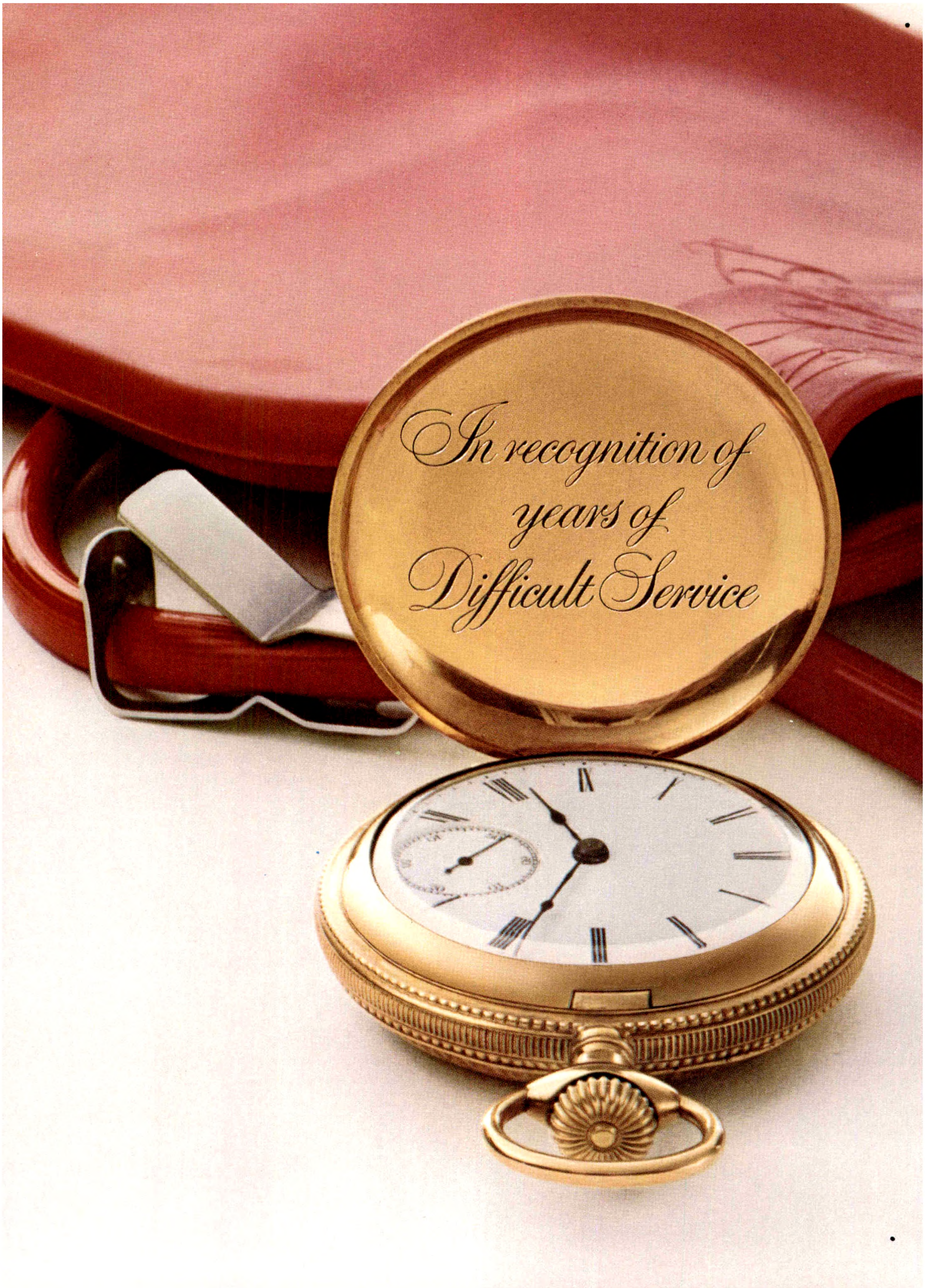
A.R.D®
STERILE

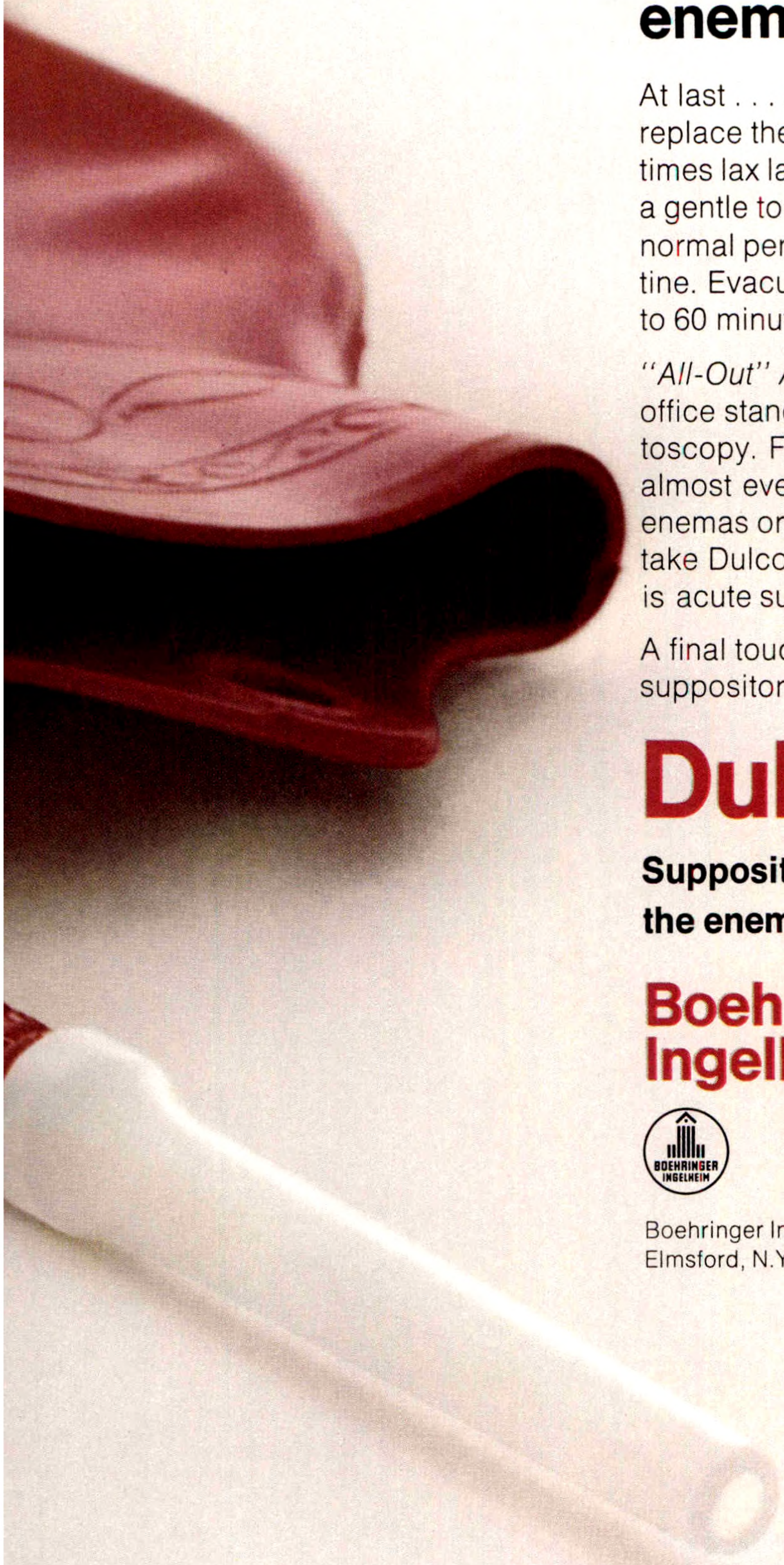
It holds in place with buttock pressure alone. So the unique, anatomically-shaped A.R.D. dressing makes changing far easier, makes the patient more comfortable. Soft and lint-free with a non-stick surface, yet highly absorbent to perspiration, wound exudates and watery fecal discharge. An excellent vehicle for topical medication. Supplied sterile in dispenser nest of 24 dressings. Write for a free clinical trial supply. Pat. No. 2,742,042 Re. 24,385

FULLER SHIELD®
THE QUICK-CHANGE T-BINDER SUBSTITUTE

It protects against soiling of bed-linen or clothing, holds anal, perianal and pilonidal dressings comfortably in place. Snap open front and quick open fasteners on belt make changing easier.
Pat. No. 3,247,846

fuller®
FULLER LABORATORIES, INC.
Eden Prairie, Minnesota 55343


In recognition of
years of
Difficult Service



Dulcolax retires the enema...

At last . . . a gentle and reliable way to replace the appalling enema. Or the sometimes lax laxative. Dulcolax suppositories put a gentle touch on the colon, producing normal peristalsis throughout the large intestine. Evacuation usually occurs within 15 to 60 minutes.

"All-Out" Action: Dulcolax is a hospital/office standby for surgery, radiology, proctoscopy. For constipation, acute or chronic, almost everyone will prefer Dulcolax to enemas or laxatives. And almost anyone can take Dulcolax . . . its only contraindication is acute surgical abdomen.

A final touch: Dulcolax comes in both suppositories and tablets.

Dulcolax® bisacodyl NF

Suppositories...to replace the enema

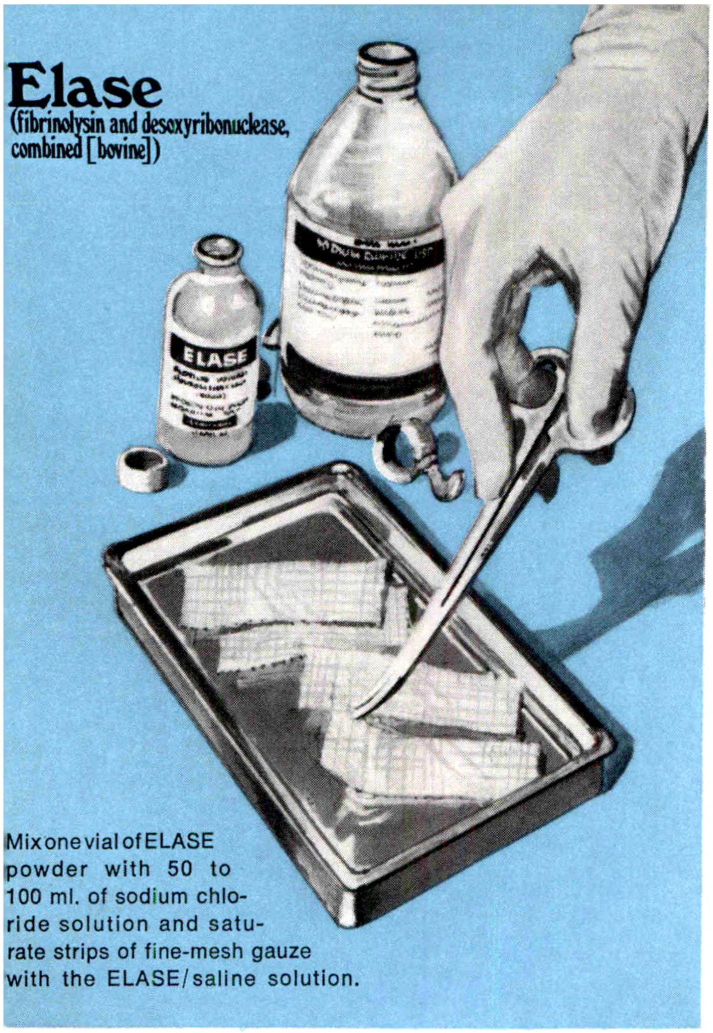
Boehringer Ingelheim

BOEHRINGER INGELHEIM

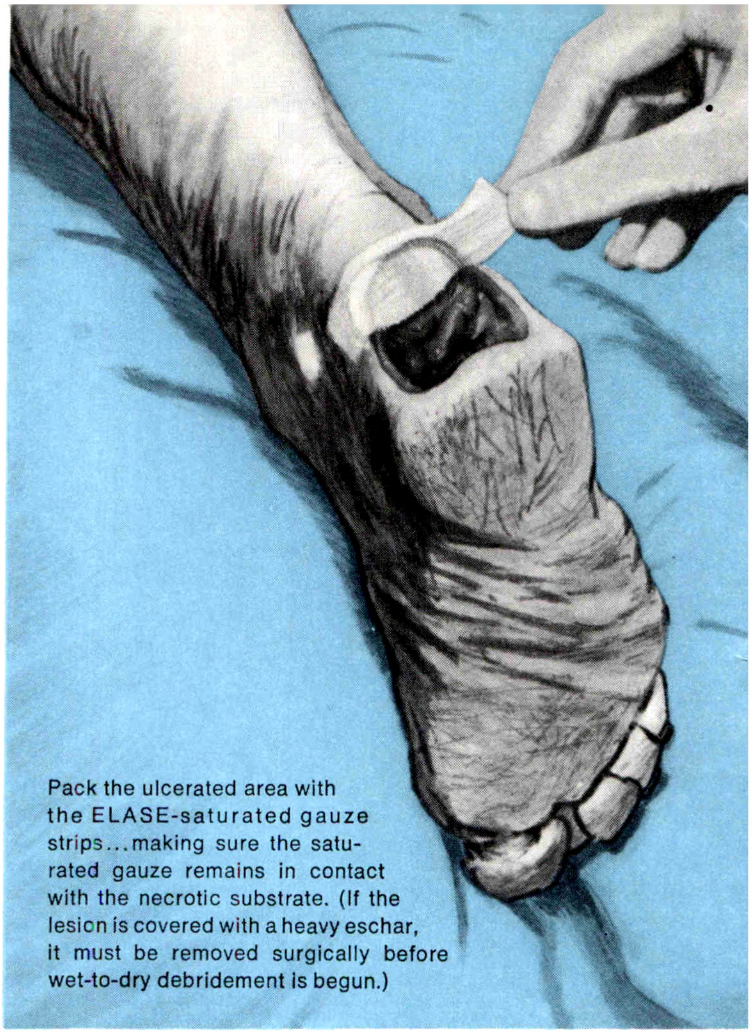
Boehringer Ingelheim Ltd.
Elmsford, N.Y. 10523

Elase

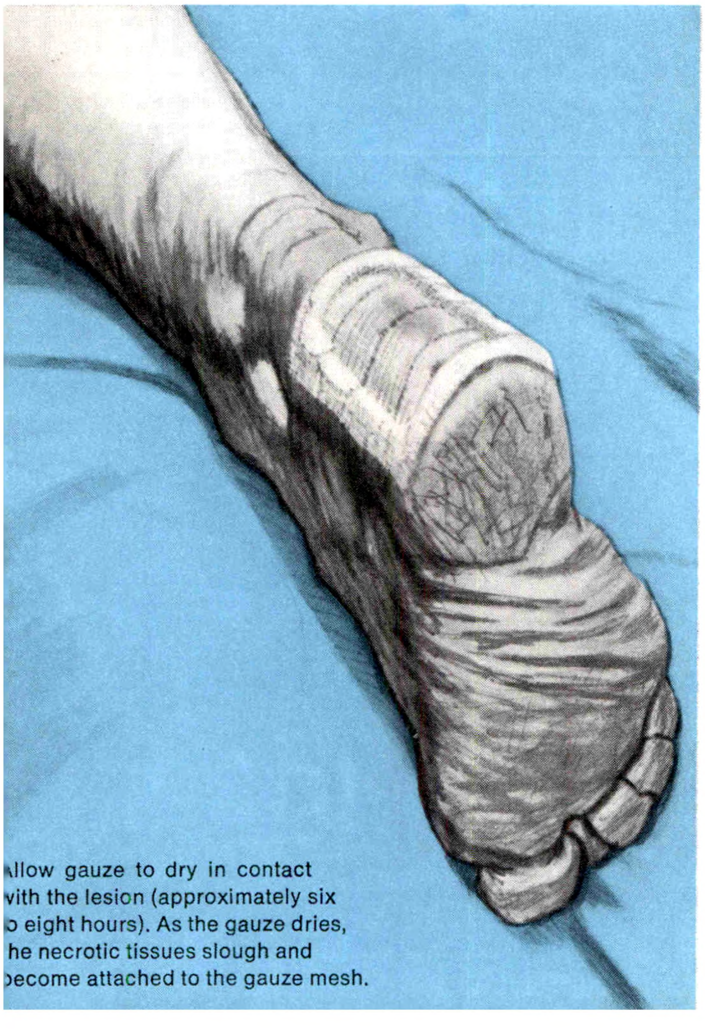
(fibrinolysin and desoxyribonuclease, combined [bovine])



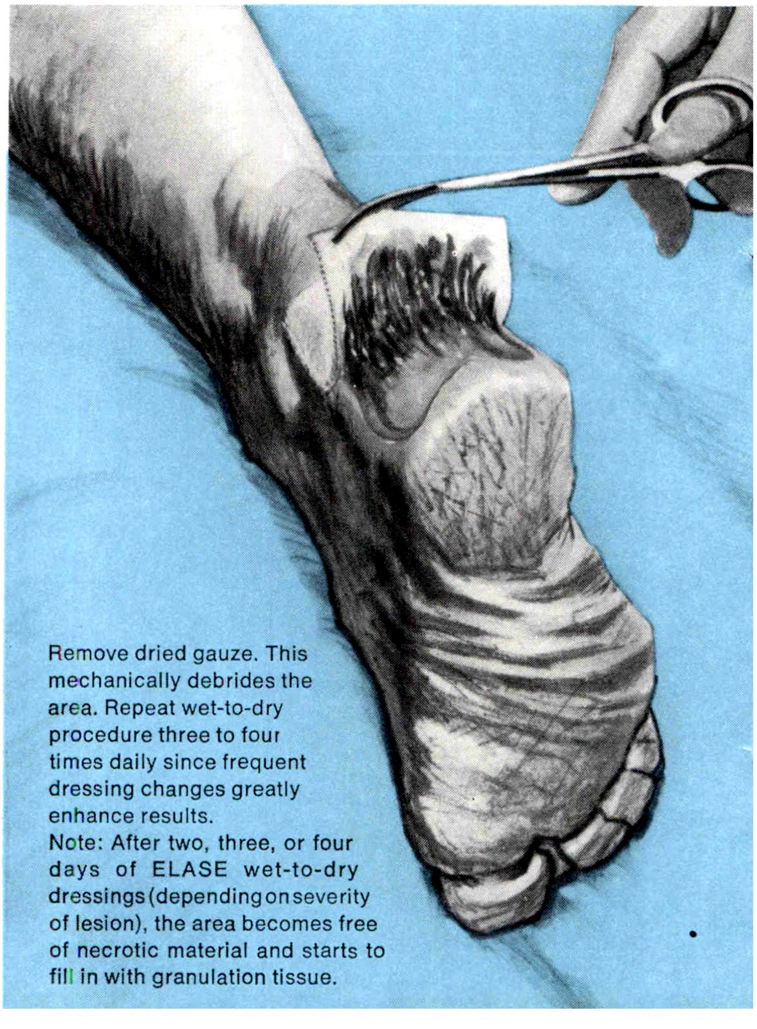
Mix one vial of ELASE powder with 50 to 100 ml. of sodium chloride solution and saturate strips of fine-mesh gauze with the ELASE/saline solution.



Pack the ulcerated area with the ELASE-saturated gauze strips... making sure the saturated gauze remains in contact with the necrotic substrate. (If the lesion is covered with a heavy eschar, it must be removed surgically before wet-to-dry debridement is begun.)



llow gauze to dry in contact
ith the lesion (approximately six
o eight hours). As the gauze dries,
he necrotic tissues slough and
ecome attached to the gauze mesh.



Remove dried gauze. This mechanically debrides the area. Repeat wet-to-dry procedure three to four times daily since frequent dressing changes greatly enhance results.

Note: After two, three, or four days of ELASE wet-to-dry dressings (depending on severity of lesion), the area becomes free of necrotic material and starts to fill in with granulation tissue.

the new way is wet-to-dry ...debridement with

Elase® solution

(fibrinolysin and desoxyribonuclease, combined [bovine])

INDICATIONS: Elase is indicated for topical debridement in general surgical wounds, ulcerative lesions, burns, circumcision and episiotomy, and in cervicitis and vaginitis. Elase is used as an irrigating agent in infected wounds, otorhinolaryngologic wounds, and superficial hematomas (except when the hematoma is adjacent to or within adipose tissue).

CONTRAINDICATIONS: Elase is contraindicated in individuals with a history of hypersensitivity reactions to any of the components. Elase is not recommended for parenteral use since the bovine fibrinolysin may be antigenic.

PRECAUTIONS: The usual precautions against allergic reactions should be observed, particularly in persons with a history of sensitivity to materials of bovine origin or to mercury compounds.
To be maximally effective, Elase solutions must be freshly prepared before use. The loss in activity is reduced by refrigeration; however, even when stored in a refrigerator, the solution should not be used 24 hours or more after reconstitution.

ADVERSE REACTIONS: Side effects attributable to the enzymes have not been a problem at the dose and for the indications recommended. With higher concentrations, local hyperemia may be a side effect.

HOW SUPPLIED: Elase (powder) is supplied dried in 30-cc. rubber-diaphragm-capped vials containing 25 units (Loomis) of fibrinolysin and 15,000 units (modified Christensen method) of desoxyribonuclease with 0.1 mg. thimerosal (mercury derivative).
Elase Ointment is supplied in 30-Gm. tubes containing 30 units (Loomis) of fibrinolysin and 20,000 units of desoxyribonuclease with 0.12 mg. thimerosal and in 10-Gm. tubes containing 10 units of fibrinolysin and 6,666 units of desoxyribonuclease with 0.04 mg. thimerosal.

PARKE-DAVIS

Parke, Davis & Company, Detroit, Michigan 48232

HF PA 593 102171

on the surgical service...

more than 10 years of clinical experience★

Keflin® I.V.
sodium cephalothin
2 Gm.* in 100-ml. ampoule
for sepsis and pneumonias[†]

Over the years, Keflin has been, and continues to be, a logical choice of surgeons for the treatment of sepsis and pneumonias with or without septicemia or shock when due to susceptible strains of *Klebsiella, Escherichia coli,* and *Proteus mirabilis. Pseudomonas* is resistant; many strains of enterococci, such as *Streptococcus faecalis,* are relatively resistant. Keflin is contraindicated in persons who have shown hypersensitivity to cephalosporins and should be used with great caution in patients allergic to penicillin.

The prompt administration of Keflin has proved to be useful in the hospital for the treatment of sepsis, particularly if shock is present or impending. Furthermore, it may even be given to:

- patients with impaired renal function, at reduced dosage
- patients with low host resistance
- those with coexisting complications, such as malnutrition, trauma, and malignancy

Since the introduction of Keflin, the susceptibilities of commonly encountered organisms, as measured by in-vitro methods, have not changed significantly.

*equivalent to cephalothin
†due to susceptible organisms
★Keflin was made available for clinical investigation early in 1962 and was marketed on September 4, 1964.

300560

Lilly

Please turn page for prescribing information.

Description: Keflin® (sodium cephalothin, Lilly) is a semisynthetic cephalosporin antibiotic for parenteral use. It is the sodium salt of 7-(thiophene-2-acetamido) cephalosporanic acid. The sodium content is 55 mg. per Gm. of cephalothin.

Actions: *Microbiology*—The bactericidal action of cephalothin results from inhibition of cell-wall synthesis. In-vitro and in-vivo activity has been demonstrated against strains of the following micro-organisms:

- *Staphylococcus aureus* (penicillin-sensitive and penicillinase-producing)
- Beta-hemolytic and other streptococci (many strains of enterococci, e.g., *Streptococcus faecalis,* are relatively resistant)
- Pneumococci
- Clostridia
- *Hemophilus influenzae*
- *Neisseria gonorrhoeae*
- *Escherichia coli* and other coliform bacteria
- *Klebsiella-Enterobacter* sp.
- *Proteus*
- *Salmonella* sp.
- *Shigella* sp.

Indications: Keflin is indicated in the treatment of serious infections of the respiratory tract, genito-urinary tract, soft tissue and skin, gastro-intestinal tract, bones and joints, bloodstream, and cardiovascular system due to susceptible organisms. Also, it has been effective in cases of peritonitis, septic abortion, and staphylococcal and pneumococcal meningitis. Effectiveness has not been established in other types of meningeal infection.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Keflin.

Contraindication: Keflin is contraindicated in persons who have shown hypersensitivity to cephalosporin antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN C DERIVATIVES SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS. INSTANCES OF PATIENTS WHO HAVE HAD SEVERE REACTIONS TO BOTH DRUGS, INCLUDING DEATH FROM ANAPHYLAXIS, HAVE BEEN REPORTED.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exception should be made with regard to Keflin.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions: Patients should be followed carefully so that any side-effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to Keflin occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine, antihistamines, pressor amines, or corticosteroids).

When Keflin is administered to patients with transient or persistent reduction of urinary output due to impaired renal function, the total daily dose should be reduced. Careful clinical observation and laboratory studies should be made, because higher and more prolonged systemic antibiotic concentrations can occur (see Administration and Dosage below).

When intravenous doses of cephalothin larger than 6 Gm. daily are given by infusion for periods longer than three days, they may be associated with thrombophlebitis, and the veins may have to be alternated. The addition of 10 to 25 mg. of hydrocortisone to intravenous solutions containing 4 to 6 Gm. of cephalothin may reduce the incidence of thrombophlebitis. The use of small I.V. needles in the larger available veins may be preferred.

Prolonged use of Keflin® (sodium cephalothin, Lilly) may result in the overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest® tablets but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: *Hypersensitivity*—Maculopapular rash, urticaria, reactions resembling serum sickness, and anaphylaxis have been reported. Eosinophilia and drug fever have been observed to be associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—Neutropenia and hemolytic anemia have been reported. Some individuals, particularly those with azotemia, have developed positive direct Coombs tests during cephalothin therapy.

Liver—Transient rise in SGOT has been noted.

Kidney—Rise in BUN has been observed; however, some patients with elevated BUN at the beginning of cephalothin therapy have had values return to normal during treatment.

Local Reactions—Pain, induration, tenderness, and elevation of temperature have been reported following repeated intramuscular injections. Thrombophlebitis has occurred and is usually associated with daily doses of over 6 Gm. given by infusion for more than three days.

Administration and Dosage: *In adults,* the usual dosage range is 500 mg. to 1 Gm. of cephalothin every four to six hours. A dosage of 500 mg. every six hours is adequate in uncomplicated pneumonia, furunculosis with cellulitis, and most urinary tract infections. In severe infections, this may be increased by giving the injections every four hours or, when the desired response is not obtained, by raising the dose to 1 Gm. In life-threatening infections, doses up to 2 Gm. every four hours may be required.

In infants and children, the dosage should be proportionately less in accordance with age, weight, and severity of infection. Daily administration of 50 mg. per Kg. (40 to 80 mg. per Kg. or 20 to 40 mg. per pound) in divided doses has been found effective for most infections susceptible to Keflin.

For additional information regarding dosage and administration, see package literature.

How Supplied: Ampoules Keflin® (Sterile Sodium Cephalothin, U.S.P.), equivalent to 1 Gm. cephalothin, 10-ml. size, rubber-stoppered, in packages of 1 and eggcrate cartons of 25; equivalent to 2 Gm. cephalothin, 100-ml. size, rubber-stoppered, in packages of 1 and eggcrate cartons of 10; equivalent to 4 Gm. cephalothin, 50-ml. size, rubber-stoppered, in packages of 1 and eggcrate cartons of 10. [013173]

on the surgical service...

Keflin® I.V.

sodium cephalothin

2 Gm.* in 100-ml. ampoule

*equivalent to cephalothin

10 years of
clinical
experience

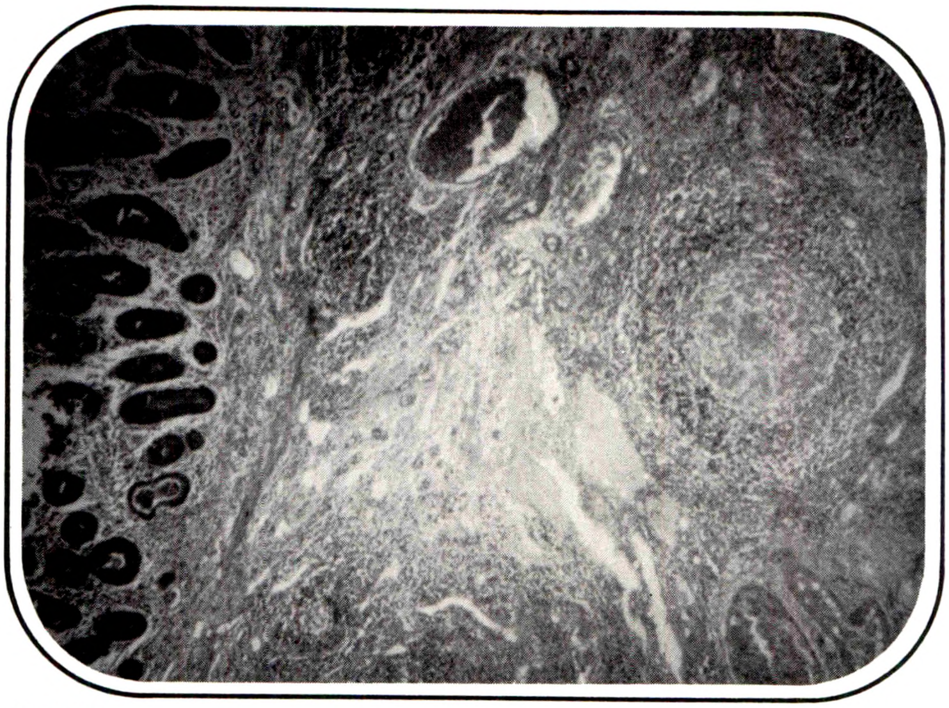
Additional information
available to the
profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

Lilly

300767

• active
granulomatous
or ulcerative
colitis?*



In any case...
when nutritional
supplementation
is indicated

Berocca® is therapy
tablets

With balanced, high potency B-complex and C vitamins... No odor... Virtually no aftertaste... Lowest priced Rx formula.

Please see complete product information, a summary of which follows:

Each Berocca Tablet contains:

Thiamine mononitrate (Vitamin B_1)	15 mg
Riboflavin (Vitamin B_2)	15 mg
Pyridoxine HCl (Vitamin B_6)	5 mg
Niacinamide	100 mg
Calcium pantothenate	20 mg
Cyanocobalamin (Vitamin B_{12})	5 mcg
Folic acid	0.5 mg
Ascorbic acid (Vitamin C)	500 mg

Indications: Nutritional supplementation in conditions in which water-soluble vitamins are required prophylactically or therapeutically.

Warning: Not intended for treatment of pernicious anemia or other primary or secondary anemias. Neurologic involvement may develop or progress, despite temporary remission of anemia, in patients with pernicious anemia who receive more than 0.1 mg of folic acid per day and who are inadequately treated with vitamin B_{12}.

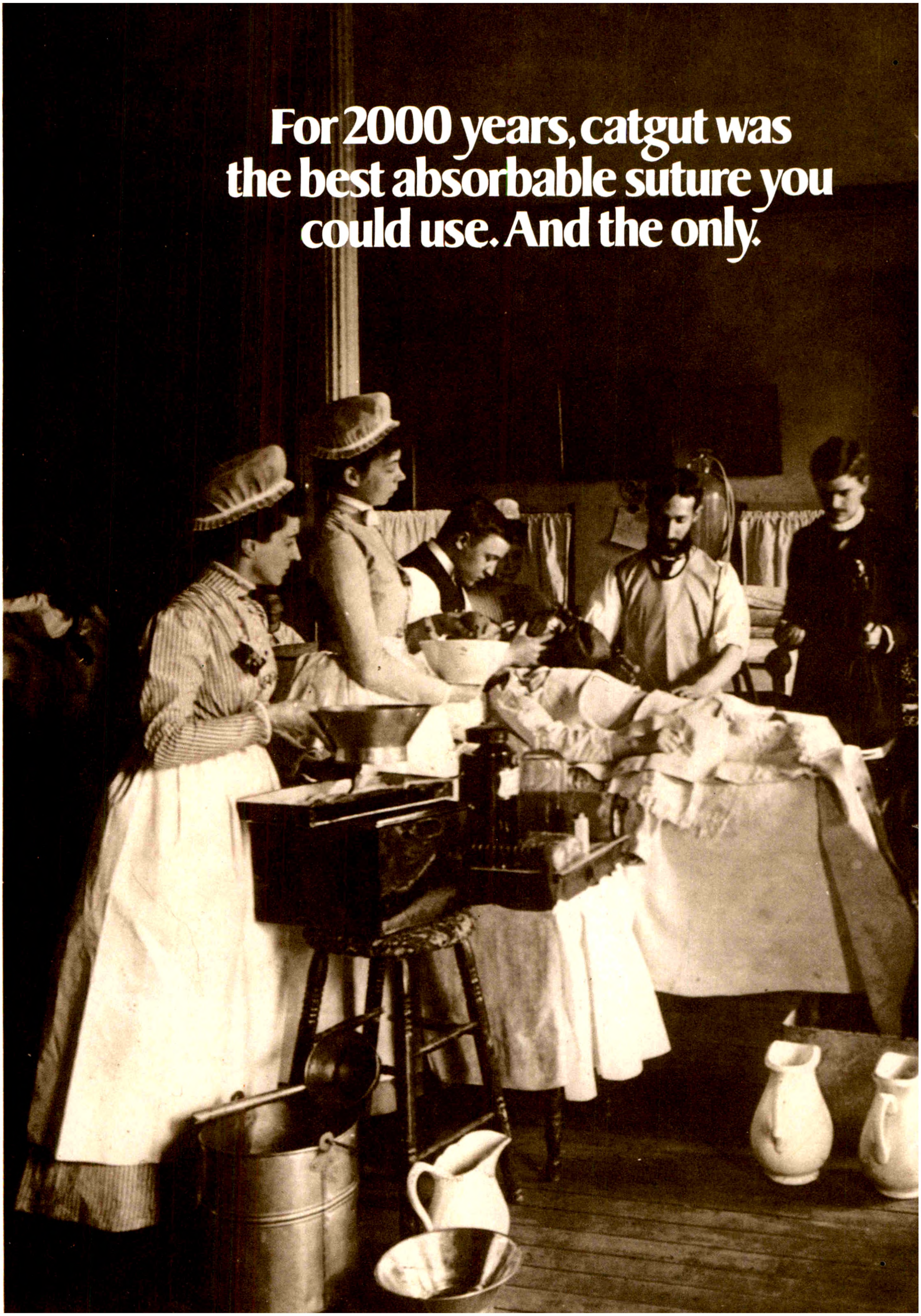
Dosage: 1 or 2 tablets daily, as indicated by clinical need.

Available: In bottles of 100.

ROCHE

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

*Granulomatous colitis is revealed in this photomicrograph. Diagnostic signs show full thickness involvement of the bowel wall, including mucosa and muscularis, by a granulomatous inflammatory process. In ulcerative colitis, a nongranulomatous inflammation is present, generally limited to the mucosa.


For 2000 years, catgut was the best absorbable suture you could use. And the only.

But that was before DEXON® polyglycolic acid suture.

Down through the centuries, gut generally did a decent enough job. Generally. But now there's DEXON. This is a suture you can count on. For strength. For predictable absorption. For minimal tissue reaction. For ease of handling.

Let your Davis & Geck salesman prove to you how excellent DEXON is. He'll show you that, with DEXON, tomorrow's suture is already here.

The future is with
DEXON®

See next page for
complete product information.

**Complete Product Information—
Approved Official Package Insert**

DESCRIPTION DEXON® polyglycolic acid Suture—Synthetic, Absorbable is a homopolymer of glycolic acid. The sutures are sterile, inert, noncollagenous, nonantigenic, nonpyrogenic, flexible, braided, undyed with a natural beige color. They are uniform in size and tensile strength, but are smaller in diameter than Absorbable Surgical Sutures of equivalent tensile strength.

ACTIONS When DEXON is placed in tissues, a minimal tissue reaction occurs which is followed by a microscopic layer of fibrous connective tissue which grows into the suture material. Clinical experience, confirmed by animal studies, revealed no absorption at 7 days, minimal absorption at 15 days, maximum absorption at 30 days, and essentially complete resorption after 60 to 90 days. Therefore, the suture may be expected to maintain optimum strength during the critical early postoperative healing phase.

INDICATIONS This suture may be used in blood vessel ligation or tissue repair, including skin, where absorbable or nonabsorbable sutures are required. The suture may be removed or left in place until it is completely absorbed.

CONTRAINDICATIONS Where extended approximation of tissues must be maintained.

WARNINGS The safe use of this suture in cardiovascular, neural, and ophthalmological surgery has not been established. Do not resterilize. Discard opened, unused sutures.

PRECAUTIONS As with all sutures, acceptable surgical practice must be followed with respect to drainage and closure of infected wounds. DEXON polyglycolic acid Suture—Synthetic, Absorbable requires special care in placing the first knot. In rare instances disintegration of the sutures may be prolonged.

ADVERSE REACTIONS Adverse reactions have been rare and are similar to those which occur with all sutures; they include tissue reaction or inflammation and fibrinous or granulation tissue. Wound separation and bleeding have occurred infrequently.

DOSAGE AND ADMINISTRATION
Use as required per operation.

HOW SUPPLIED Suture sizes 6-0 through 1. Supplied in cut lengths or ligating reels, non-needled or affixed to the various Davis & Geck ATRAUMATIC® needles in three dozen packages. Rev. 6/72

DAVIS+GECK
American Cyanamid Company
Pearl River, N.Y. 10965

Progress in Surgery

Editorial Board:
M. Allgöwer (Basel); *S.-E. Bergentz* (Malmö)
R.Y. Calne (Cambridge); *U.F. Gruber* (Basel)

This series of annual volumes assists general and specialized surgeons in staying informed on 'what's new in surgery' by providing original reviews from outstanding experts in their respective fields as well as frequent discussions of controversial themes by authorities expressing differing viewpoints.
The editorial board, in preparing the annual volume, selects several papers on subjects of general interest where important discoveries have recently been reported or new insight into diagnosis or therapy have brought about direct and immediate consequences for the surgeon's daily work. In sum, basic knowledge in addition to technical know-how at the postgraduate level is transmitted through the richly-illustrated volumes of 'Progress in Surgery'.

Selected Contributions Already Published in the Series
Crohn's Disease, with Special Reference to Surgical Management
Goligher, J.C., De Dombal, F.T. and *Burton, I.*
New Aspects of the Pathogenesis of Thrombo-Embolism
Nilsson, I.M. and *Isacson, S.*
Atelectasis in the Surgical Patient. Recent Conceptual Advances
Laver, M.B. and *Bendixen, H.H.*
Strictures of Bile Ducts
Smith, R.
Pathophysiological Aspects on Surgical Treatment of Thyroid Disease
Heimann, P.

For further information please request a detailed prospectus

S. Karger AG
Arnold-Böcklin-Strasse 25
CH–4011 Basel (Switzerland)

S.Karger **Basel** **München** **Paris** **London** **New York** **Sydney**

INDEX TO ADVERTISERS

PHARMACEUTICAL SUPPLIES

Abbott Laboratories
  Surbex T 15A
Boehringer Ingelheim, Ltd.
  Dulcolax 40A,41A
Burroughs Wellcome & Company
  Empirin .... Cover IV
  Polysporin 17A
Eaton Laboratories
  Furacin Topicals 37A
Knoll Pharmaceuticals
  Dilaudid 9A
  Santyl 33A,34A
Eli Lilly & Company
  Darvocet 16A
  Keflex .... 52A,Cover III
  Keflin 44A,45A,46A
  Loridine 24A,25A,26A
McGaw Laboratories
  Fre Amine 38A,39A
Purdue Frederick Company
  Senokot 4A
Reed & Carnick
  Proctofoam 2A,3A
A. H. Robins Company
  Phenaphen 18A,19A
Roche Laboratories
  Berocca 47A
  Valium 20A,21A,22A
William H. Rorer
  Maalox 7A
Wampole Laboratories
  Avazyme 11A

SUPPLIES AND EQUIPMENT

Burdick Corporation 23A
Davis & Geck
  Dexon 48A,49A,50A
Ethicon, Inc.
  Prolene 29A,30A,31A,32A
Flint Laboratories
  Travase 35A,36A
Fuller Laboratories
  ARD 39A
Parke-Davis Company
  Elase 42A,43A
  Ketalar 12A,13A,14A
  Surgical Instruments .... Cover II
Purdue Frederick Company
  Betadine Ointment 1A
  Betadine Surgical 65A
Sparta Instrument Corporation 27A
Edward Weck & Co., Inc. 28A

MISCELLANEOUS

S. Karger Ag 50A
J. B. Lippincott Company 51A

COLLECTORS ITEM

ANNALS
of
SURGERY

3 Volume set of Minutes of
The American Surgical Association
1880 to 1968

J. B. Lippincott Co., c/o J. W. Bradley
East Washington Sq., Phila., Pa. 19105.

____ YES, send 3 Volume set $50.00
(postage paid)

Name ____________________
PLEASE PRINT

Address ____________________

City ____________ State ________ Zip ______

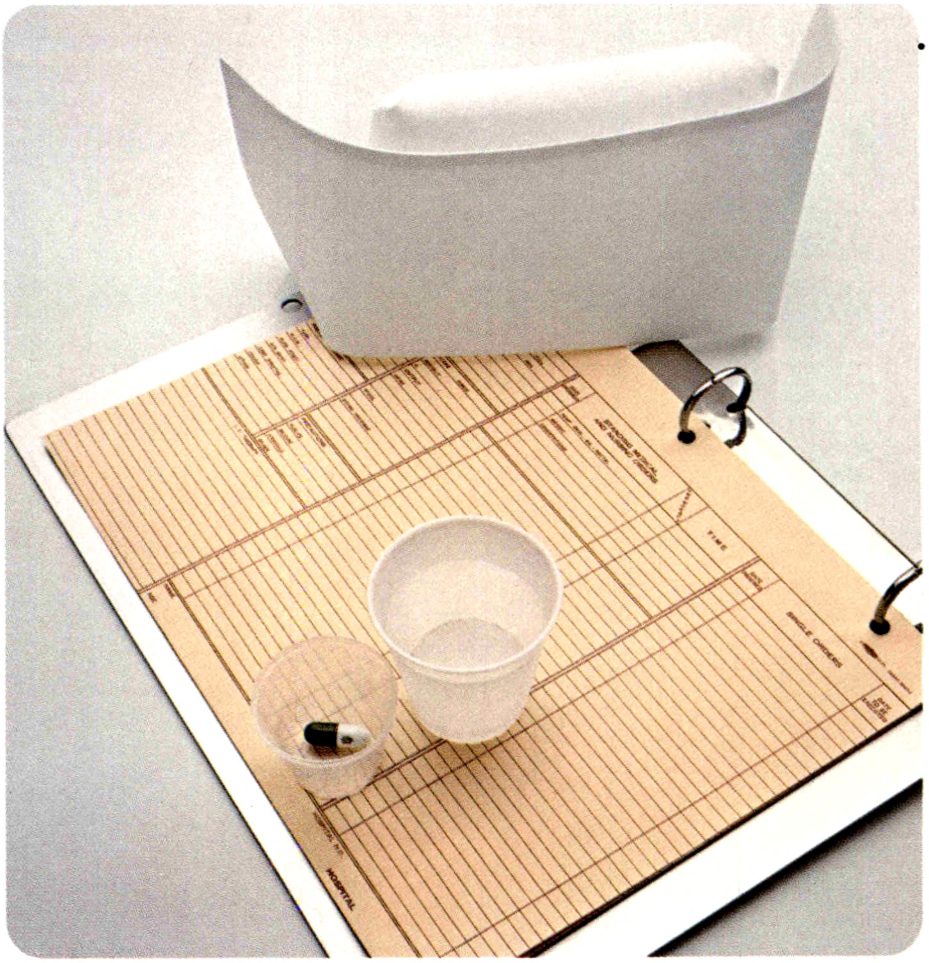
CHANGE OF ADDRESS

Change of Address: Please allow 60 days before date of issue for change of address. Notification should include the old as well as the new address, with indication of whether the change is temporary or permanent. Please give the name of the *Journal.*

Send Change of Address cards to:

ANNALS OF SURGERY
c/o Fulfillment Manager
East Washington Square
Philadelphia, Penna. 19105

so important
in the hospital



just as useful
in the office

Clinical trial experience

Clinical trials establish the usefulness of Keflex in both the hospital and the office.

Effective in an important range of infections

Keflex is appropriate in a variety of infections that are treated in office practice:

Respiratory infections, such as bronchitis, pneumonia, and bronchopneumonia, due to susceptible strains of *Diplococcus pneumoniae*

Urinary tract infections caused by susceptible strains of *Escherichia coli, Proteus mirabilis*, or *Klebsiella* sp.

Skin and soft-tissue infections due to susceptible strains of staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains

High blood levels, bactericidal activity in vitro

With Keflex, peak serum levels are reached in one hour. For example, following a single 500-mg. dose, average peak serum levels are approximately 18 mcg. per ml.

In addition, in-vitro studies demonstrate that the cephalosporins exhibit bactericidal activity (by inhibition of cell-wall synthesis) against susceptible organisms. (The in-vivo mechanism cannot be determined, of course, because no method exists for clinical demonstration.)

Acid stable, rapidly absorbed

Because Keflex is acid stable, it may be given without regard to meals. Furthermore, it is rapidly absorbed after oral administration.

A good choice in the office

There are a host of reasons for prescribing Keflex with confidence in the office. That's why it is so often a good first choice when indicated.

Note: Keflex is contraindicated in patients with known allergy to cephalosporins and should be used with great caution in patients allergic to penicillin. The most frequent side-effects are gastro-intestinal.

Prescribing Information

Description: Keflex is a semisynthetic cephalosporin antibiotic intended for oral administration. It is 7-(D-α-amino-α-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid, monohydrate.

Actions: *Human Pharmacology*—Keflex is acid stable and may be given without regard to meals. It is rapidly absorbed after oral administration. Following doses of 250 and 500 mg., average peak serum levels of approximately 9 to 18 mcg. per ml. respectively were obtained at one hour. Measurable levels were present six hours after administration. Over 90 percent of the drug is excreted unchanged in the urine within eight hours. Peak urine concentrations are approximately 1,000 mcg. per ml. during this period following a 250-mg. dose.

Microbiology—In-vitro tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Keflex is active against the following organisms in vitro:

Beta-hemolytic streptococci/Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains/*Diplococcus pneumoniae/Escherichia coli/Proteus mirabilis/Klebsiella* sp.

Note—Most strains of enterococci *(Streptococcus faecalis)* and a few strains of staphylococci are resistant to Keflex. It is not active against most strains of *Enterobacter* sp., *Pr. morganii*, and *Pr. vulgaris*. It has no activity against *Pseudomonas* or *Herellea* species. When tested by in-vitro methods, staphylococci exhibit cross-resistance between Keflex and methicillin-type antibiotics.

Indications: Keflex is indicated for the treatment of the following infections when caused by susceptible strains of the designated micro-organisms:

Respiratory tract infections caused by *D. pneumoniae* and group A beta-hemolytic streptococci (Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Keflex is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of Keflex in the subsequent prevention of rheumatic fever are not available at present.)

Skin and soft-tissue infections caused by staphylococci and/or streptococci

Genito-urinary tract infections, including acute prostatitis, caused by *Esch. coli, Pr. mirabilis*, and *Klebsiella* sp.

Note—Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

Contraindication: Keflex is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORIN C DERIVATIVES SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exception should be made with regard to Keflex.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions: Patients should be followed carefully so that any side-effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to Keflex occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine, antihistamines, pressor amines, or corticosteroids).

Prolonged use of Keflex may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

Keflex should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

As a result of administration of Keflex, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: *Gastro-Intestinal*—The most frequent side-effect has been diarrhea. It was very rarely severe enough to warrant cessation of therapy. Nausea, vomiting, dyspepsia, and abdominal pain have also occurred.

Hypersensitivity—Allergies (in the form of rash, urticaria, and angioedema) have been observed. These reactions usually subsided upon discontinuation of the drug.

Other reactions have included genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, and headache. Eosinophilia, neutropenia, and slight elevations in SGOT and SGPT have been reported.

Administration and Dosage: Keflex is administered orally. The adult dosage ranges from 1 to 4 Gm. daily in divided doses. The usual adult dose is 250 mg. every six hours. For more severe infections or those caused by less susceptible organisms, larger doses may be needed. If daily doses of Keflex greater than 4 Gm. are required, parenteral cephalosporins, in appropriate doses, should be considered.

The recommended daily dosage for children is 25 to 50 mg. per Kg. divided into four doses.

In severe infections, the dosage may be doubled.

In the treatment of beta-hemolytic streptococcal infections, a therapeutic dosage of Keflex should be administered for at least ten days.

How Supplied: Pulvules® Keflex® (cephalexin monohydrate, Lilly), equivalent to 250 or 500 mg. cephalexin, in bottles of 24 and 100 and in Identi-Dose® (unit dose medication, Lilly) in boxes of 100.

Keflex, for Oral Suspension, equivalent to 125 mg. cephalexin per 5-ml. teaspoonful, in 60 and 100-ml.-size packages and in Identi-Dose in packages of 100.

Keflex, for Pediatric Drops, equivalent to 100 mg. cephalexin per ml. (5 mg. per drop), in 10-ml.-size packages, with dropper calibrated at 25 and 50 mg. [121172]

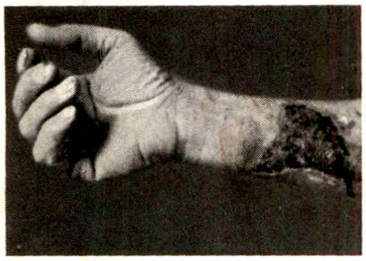
Keflex® 250-mg. Pulvules®
cephalexin monohydrate
so often a good first choice

Additional information available to the profession on request.
Eli Lilly and Company • Indianapolis, Indiana 46206

Lilly

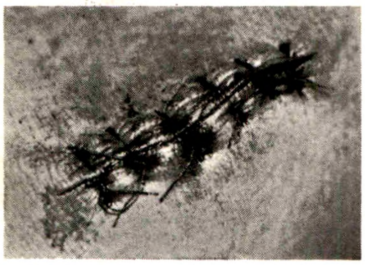
300941

HERE Burns



When parenteral analgesia is no longer required, Empirin Compound with Codeine usually provides the relief needed.

HERE Sutures



Empirin Compound with Codeine is effective for visceral as well as soft tissue pain—provides an antitussive bonus in addition to its prompt, predictable analgesia.

CIII **prescribing convenience:** up to 5 refills in 6 months, at your discretion (unless restricted by state law); by telephone order in many states.

Empirin Compound with Codeine **No. 3,** codeine phosphate* 32.4 mg. (gr. ½); **No. 4,** codeine phosphate* 64.8 mg. (gr. 1). *Warning—may be habit-forming. Each tablet also contains: aspirin gr. 3½, phenacetin gr. 2½, caffeine gr. ½.

Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

Healing nicely, but it still HURTS

EMPIRIN® COMPOUND c̄ CODEINE

#3, codeine phosphate* (32.4 mg.) gr. ½
#4, codeine phosphate* (64.8 mg.) gr. 1

AUGUST 1973 • VOL. 178, NO. 2
ANSUA5

ANNALS
of
SURGERY

A Monthly Review of
Surgical Science and Practice
Since 1885

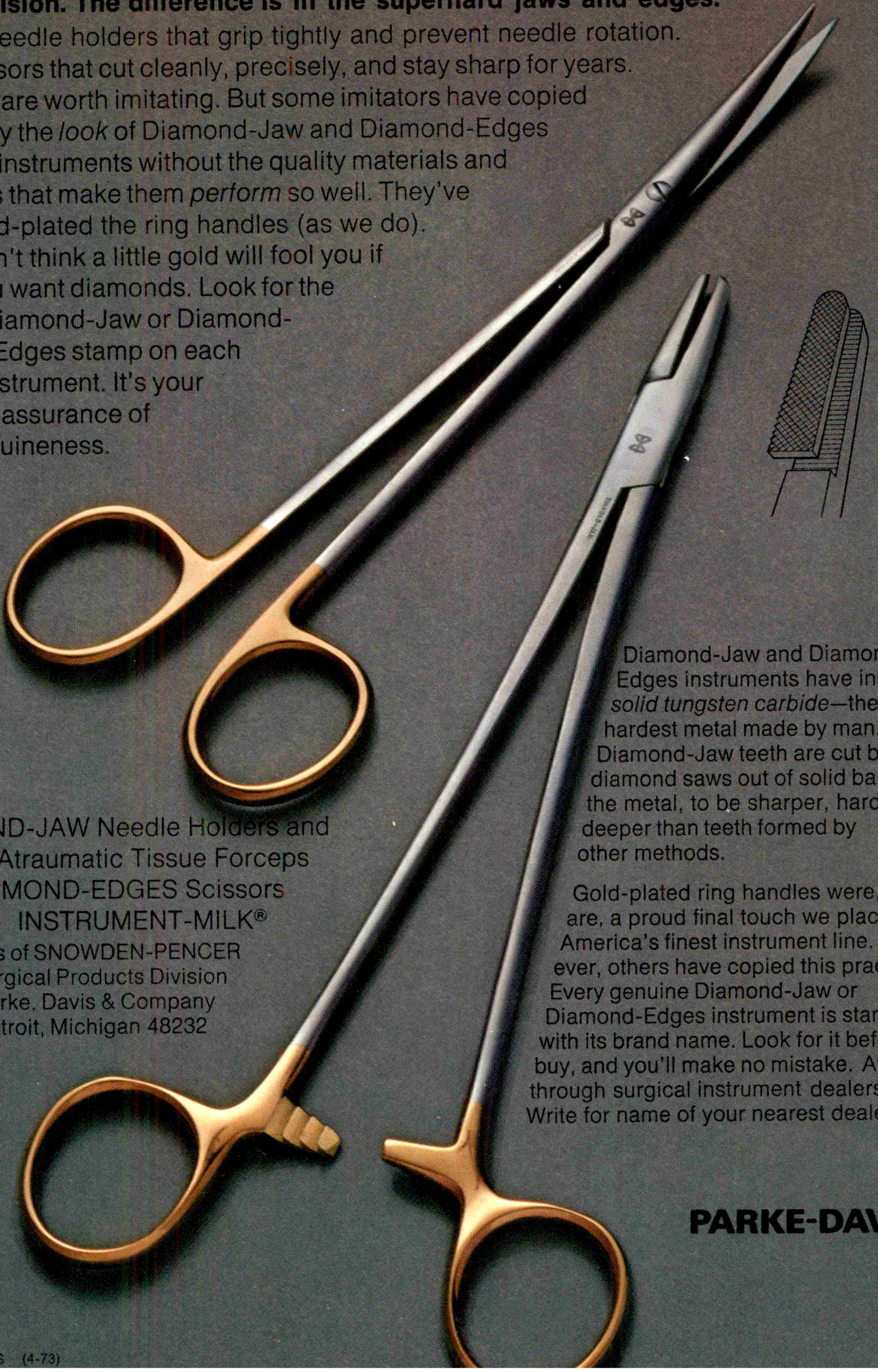
LIBRARY
OF MEDICINE

J. B. LIPPINCOTT COMPANY

Don't mistake gold for diamonds

There is only one true line of DIAMOND-JAW® and DIAMOND-EDGES® instruments, made by our Snowden-Pencer Medical-Surgical Products Division. The difference is in the superhard jaws and edges.

Needle holders that grip tightly and prevent needle rotation. Scissors that cut cleanly, precisely, and stay sharp for years. These are worth imitating. But some imitators have copied only the *look* of Diamond-Jaw and Diamond-Edges instruments without the quality materials and processes that make them *perform* so well. They've gold-plated the ring handles (as we do). But we don't think a little gold will fool you if you want diamonds. Look for the Diamond-Jaw or Diamond-Edges stamp on each instrument. It's your assurance of genuineness.



Diamond-Jaw and Diamond-Edges instruments have inserts of *solid tungsten carbide*—the hardest metal made by man. Diamond-Jaw teeth are cut by diamond saws out of solid bars of the metal, to be sharper, harder, deeper than teeth formed by other methods.

Gold-plated ring handles were, and still are, a proud final touch we place on America's finest instrument line. However, others have copied this practice. Every genuine Diamond-Jaw or Diamond-Edges instrument is stamped with its brand name. Look for it before you buy, and you'll make no mistake. Available through surgical instrument dealers. Write for name of your nearest dealer.

DIAMOND-JAW Needle Holders and
Atraumatic Tissue Forceps
DIAMOND-EDGES Scissors
INSTRUMENT-MILK®
Products of SNOWDEN-PENCER
Medical-Surgical Products Division
Parke, Davis & Company
Detroit, Michigan 48232

PARKE-DAVIS

PD-JA-0937-1-MS (4-73)

14.1.74

Now! Microbicidal power in convenient

BETADINE "disposables"

BETADINE Antiseptic Gauze Pad
BETADINE Solution Swabsticks
BETADINE Solution Swab Aid

BETADINE Antiseptic Gauze Pad

Topical microbicidal dressing (3" x 9") impregnated with the same active ingredient as in BETADINE Solution...for prevention and treatment of surface infections ...degerming the skin and disinfecting wounds, burns, lacerations and abrasions.

BETADINE
Solution Swab Aid

Small single-use antiseptic pad for prompt degerming of small skin areas prior to such procedures as injections, aspirations, catheterization and surgery . . . and in cuts, minor wounds, burns, lacerations and abrasions.

BETADINE
Solution Swabsticks

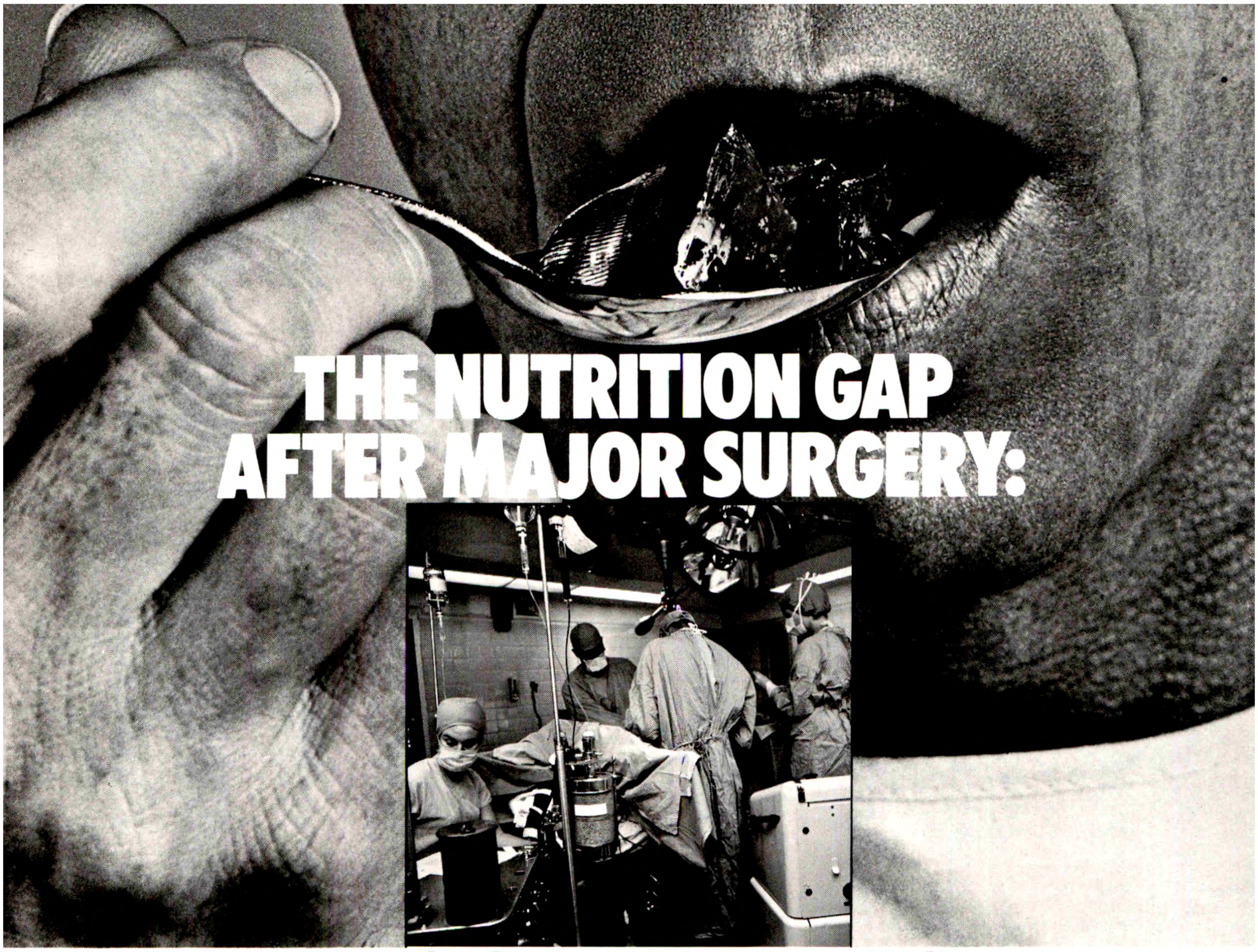
Antiseptic applicator tips for hard-to-reach smaller sites, including folds and creases. Use for degerming the skin prior to injections, aspirations, surgery, urinary catheterization; in disinfection of skin in minor wounds; in preoperative oral tissue degerming; preparing skin for dressing changes.

UNIVERSITY [illegible] MEDICINE
LIBRARY
C. U.

• BETADINE SECURITY ZONE • APOLLO LUNAR MISSION

Purdue Frederick

©COPYRIGHT 1973, THE PURDUE FREDERICK COMPANY/NORWALK, CONN. 06856 A7004 123873



It can make the patient eat himself alive.

After major surgery, the patient may burn up 3000 Calories a day. Clear liquid diets given after such surgery supply a few hundred Calories... and very little else. To make up the energy deficit, patients soon start to consume their own body protein.

With Vivonex HN you can give the patient 3000 Calories, 20 grams of usable nitrogen (equal to 125 grams of usable protein), and a balanced diet of elemental nutrients each day. (Evidence of minimal G.I. function must exist.)

Vivonex HN raises total protein levels... helps restore positive nitrogen balance... helps prevent the rapid protein wastage that may retard post operative healing and recovery.

Vivonex HN is an alternative to the risks of intravenous hyperalimentation because it consists solely of basic nutrients requiring little or no digestion: pure amino acids, simple sugars, essential fat, vitamins and minerals. Absorption takes place rapidly and completely in the upper intestine. There is no indigestible matter.

Ideal for tube feeding, Vivonex HN is easily fed through small-gauge tubes. It may also be served as a drink (Vivonex HN is unflavored).

Supplied in boxes containing ten 80-gram packets of unflavored water-soluble powder providing 3000 Calories, 20 grams of usable nitrogen and a full day's balanced nutrition, including the Recommended Daily Allowances of vitamins and minerals.

Precautions: For use only under a physician's supervision. Do not administer parenterally. Because of the high caloric contribution from carbohydrates some depleted individuals may manifest elevated blood sugar levels requiring insulin for regulation. The diet should not be used by diabetics without their physician's approval. The electrolyte content of the diet is based on requirements of normal individuals and may be excessive for patients with electrolyte imbalance. Use during pregnancy or lactation may require supplemental vitamins and minerals. Use for children under ten years may require adjusting the amount consumed daily to meet the Recommended Dietary Allowance for the age group involved. Vivonex HN High Nitrogen Diet is recommended for up to two months of continuous use. Store in a cool dry place.

Are you taking advantage of these nutritional information services?
- Eaton Nutrition Teaching Films
- The Eaton Nutrition Speakers Bureau
- Eaton In-Service Programs—Nutrition
- Intake: Perspectives in Clinical Nutrition (monographs).

Detailed information about any of these programs is available from your local Eaton Representative or direct from Eaton Laboratories.

For 'round-the-clock medical consultation on Eaton products, 'phone Norwich, New York, Area Code 607, 335-2111. © Morton-Norwich Products, Inc. 1972

® Originators of chemically defined diets
Eaton Laboratories
division of Morton-Norwich Products, Inc.
Norwich, New York 13815

You can help close this nutrition gap with

VIVONEX® HN ™

soluble powder The only chemically defined elemental high nitrogen diet.

The only oral hyperalimentation

...because patients respect your judgment, trust your experience

Darvon®
Compound-65

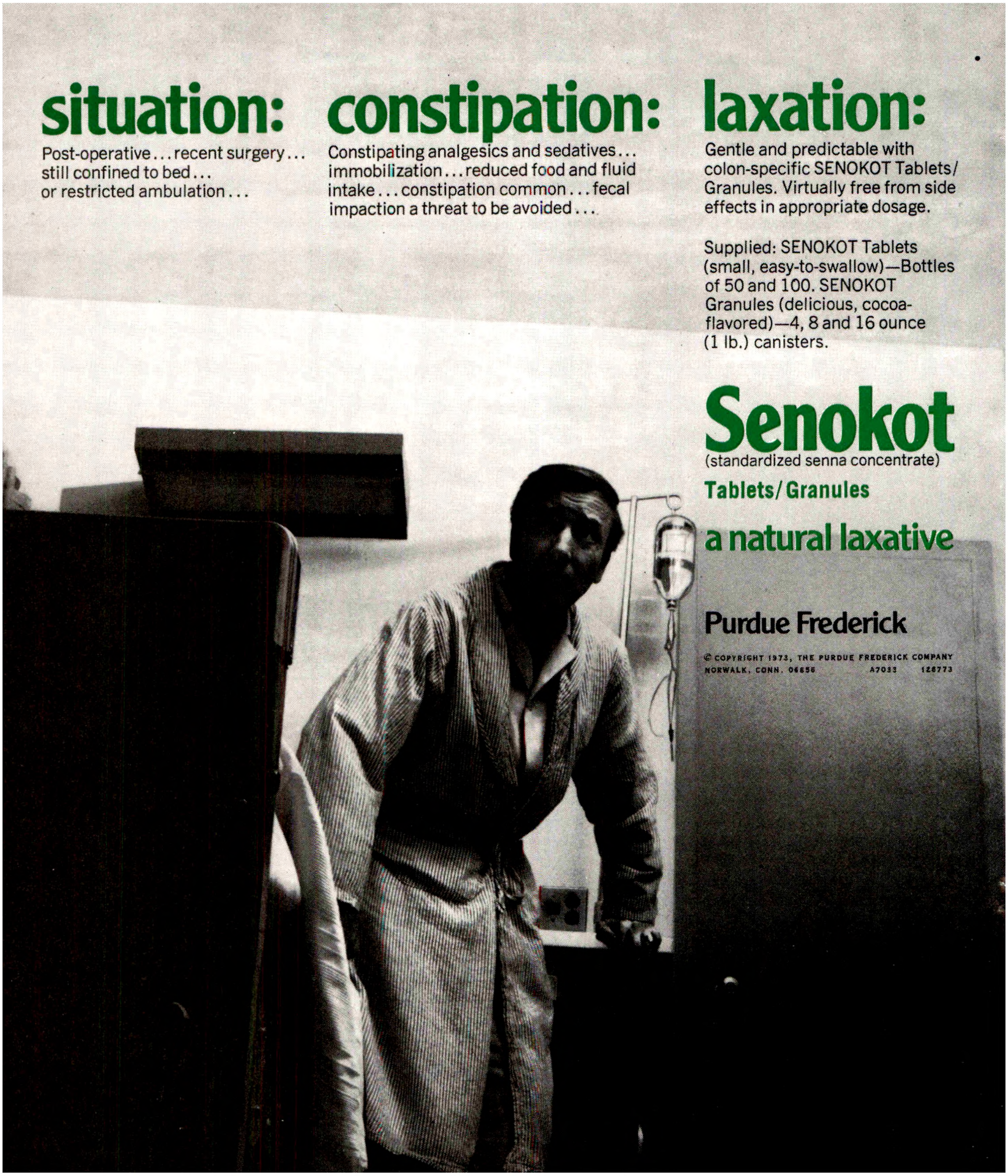
65 mg. propoxyphene hydrochloride, 227 mg. aspirin,
162 mg. phenacetin, and 32.4 mg. caffeine

made in the Lilly tradition

Lilly

Eli Lilly and Company
Indianapolis, Indiana 46206

301024



situation: Post-operative . . . recent surgery . . . still confined to bed . . . or restricted ambulation . . .

constipation: Constipating analgesics and sedatives . . . immobilization . . . reduced food and fluid intake . . . constipation common . . . fecal impaction a threat to be avoided . . .

laxation: Gentle and predictable with colon-specific SENOKOT Tablets/Granules. Virtually free from side effects in appropriate dosage.

Supplied: SENOKOT Tablets (small, easy-to-swallow)—Bottles of 50 and 100. SENOKOT Granules (delicious, cocoa-flavored)—4, 8 and 16 ounce (1 lb.) canisters.

Senokot
(standardized senna concentrate)
Tablets/Granules

a natural laxative

Purdue Frederick

© COPYRIGHT 1973, THE PURDUE FREDERICK COMPANY
NORWALK, CONN. 06856 A7033 128773

ANNALS OF SURGERY

Vol. 178 AUGUST 1973 No. 2

CONTENTS

117 Sequential System Failure after Rupture of Abdominal Aortic Aneurysms: An Unsolved Problem in Postoperative Care, *Nicholas L. Tilney*, M.D., *George L. Bailey*, M.D., *Alfred P. Morgan*, M.D., Boston, Massachusetts

123 Hemodynamics of Innominate Artery Occlusion, *David J. Mozersky*, M.D., *Robert W. Barnes*, M.D., *David S. Sumner*, M.D., *D. Eugene Strandness Jr.*, M.D., Seattle, Washington

128 Cardiac Aspects of Shock: Effects of an Ischemic Body on a Non-Ischemic Heart, *A. Mazor*, M.D., *S. Rogel*, M.D., Jerusalem, Israel

134 Surgical Management of the Dialysis Patient, *Makoto Hata*, M.D., *August R. Remmers, Jr.*, M.D., *James D. Lindley*, M.D., *Harry E. Sarles*, M.D., *Jay C. Fish*, M.D., Galveston, Texas

138 Renal Parenchymal Tolerance to Artery Occlusion: A Time and Damage Study in Rats Developing Collateral Circulation, *P. K. Donahoe*, M.D., *John D. Osmond, III*, M.D., *David R. Stewart*, M.D., *W. Hardy Hendren, III*, M.D., Boston, Massachusetts

143 Vascular Injury in Vietnam Combat Casualties: Results of Treatment at the 24th Evacuation Hospital, 1 July 1967 to 12 August 1969, *J. Judson McNamara*, M.D., *Donald K. Brief*, M.D., *Wyatt Beasley*, M.D., *John K. Wright*, M.D., Honolulu, Hawaii

148 Muscular Tumors of the Stomach: Clinical and Pathological Study of 113 Cases, *Kevin Morrissey*, M.D., *Eun Sook Cho*, M.D., *George F. Gray, Jr.*, M.D., *Bjorn Thorbjarnarson*, M.D., New York City

156 Hepatic Arterial Patency and Complications after Catheterization for Infusion Chemotherapy, *Blake Cady*, M.D., Boston, Massachusetts

162 Treatment of Primary and Secondary Liver Cancer by Hepatic Artery Ligation and Infusion Chemotherapy, *Joseph G. Fortner*, M.D., *Robert J. Mulcare*, M.D., *Ariel Solis*, M.D., *Robin C. Watson*, M.D., *Robert B. Golbey*, M.D., New York City

173 Mediastinal Hyperfunctioning Parathyroid Tumors: Review of 14 Cases, *Donald A. Scholz*, M.D., *Don C. Purnell*, M.D., *Lewis B. Woolner*, M.D., *O. Theron Clagett*, M.D., Rochester, Minnesota

179 Patho-Physiological Changes Following Ischemia of the Spleen, *M. J. Tsapogas*, M.D., *R. A. Peabody*, PH.D., *A. M. Karmody*, M.B., CH.M., *C. Chuntrasakul*, M.D., *H. Gousseous*, M.D., *C. Eckert*, M.D., Albany, New York

186 High Abdominal Aortic Aneurysm, Hepatic Artery Aneurysm, and Cystadenoma of Pancreas Treated Surgically in a Young Woman, *Benjamin F. Gibbs, Jr.*, M.D., *David R. James*, CDR., MC, USN, *Gary D. Ketron*, LCDR., MC, USNR, *Roger F. Milnes*, CAPT., MC, USN., San Diego, California

ANNALS OF SURGERY

Vol. 178 AUGUST 1973 No. 2

CONTENTS

117 Sequential System Failure after Rupture of Abdominal Aortic Aneurysms: An Unsolved Problem in Postoperative Care, *Nicholas L. Tilney,* M.D., *George L. Bailey,* M.D., *Alfred P. Morgan,* M.D., Boston, Massachusetts

123 Hemodynamics of Innominate Artery Occlusion, *David J. Mozersky,* M.D., *Robert W. Barnes,* M.D., *David S. Sumner,* M.D., *D. Eugene Strandness Jr.,* M.D., Seattle, Washington

128 Cardiac Aspects of Shock: Effects of an Ischemic Body on a Non-Ischemic Heart, *A. Mazor,* M.D., *S. Rogel,* M.D., Jerusalem, Israel

134 Surgical Management of the Dialysis Patient, *Makoto Hata,* M.D., *August R. Remmers, Jr.,* M.D., *James D. Lindley,* M.D., *Harry E. Sarles,*M.D., *Jay C. Fish,* M.D., Galveston, Texas

138 Renal Parenchymal Tolerance to Artery Occlusion: A Time and Damage Study in Rats Developing Collateral Circulation, *P. K. Donahoe,* M.D., *John D. Osmond, III,* M.D., *David R. Stewart,* M.D., *W. Hardy Hendren, III,* M.D., Boston, Massachusetts

143 Vascular Injury in Vietnam Combat Casualties: Results of Treatment at the 24th Evacuation Hospital, 1 July 1967 to 12 August 1969, *J. Judson McNamara,* M.D., *Donald K. Brief,* M.D., *Wyatt Beasley,* M.D., *John K. Wright,* M.D., Honolulu, Hawaii

148 Muscular Tumors of the Stomach: Clinical and Pathological Study of 113 Cases, *Kevin Morrissey,* M.D., *Eun Sook Cho,* M.D., *George F. Gray, Jr.,* M.D., *Bjorn Thorbjarnarson,* M.D., New York City

156 Hepatic Arterial Patency and Complications after Catheterization for Infusion Chemotherapy, *Blake Cady,* M.D., Boston, Massachusetts

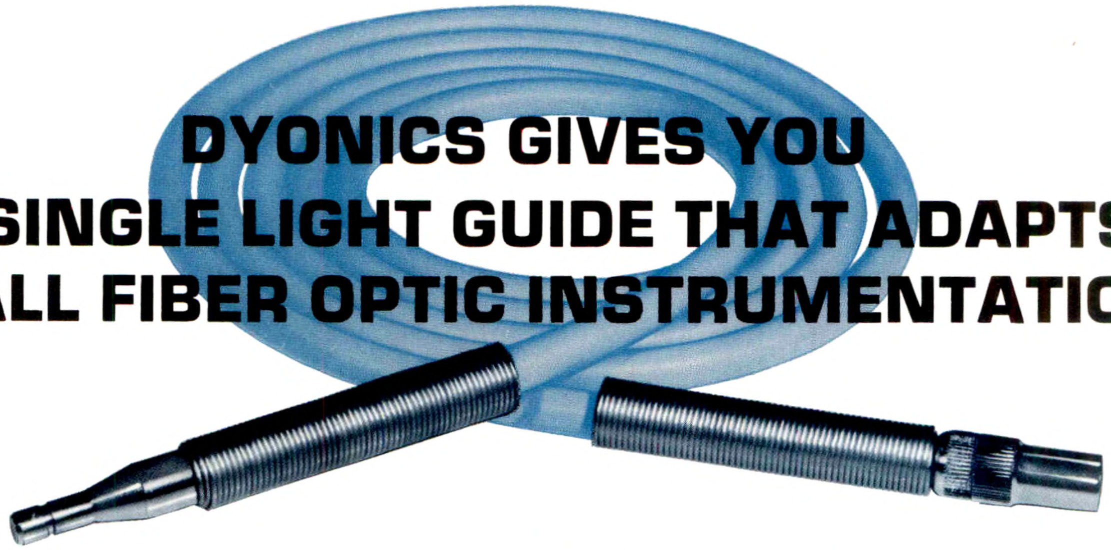
162 Treatment of Primary and Secondary Liver Cancer by Hepatic Artery Ligation and Infusion Chemotherapy, *Joseph G. Fortner,* M.D., *Robert J. Mulcare,* M.D., *Ariel Solis,* M.D., *Robin C. Watson,* M.D., *Robert B. Golbey,* M.D., New York City

173 Mediastinal Hyperfunctioning Parathyroid Tumors: Review of 14 Cases, *Donald A. Scholz,* M.D., *Don C. Purnell,* M.D., *Lewis B. Woolner,* M.D., *O. Theron Clagett,* M.D., Rochester, Minnesota

179 Patho-Physiological Changes Following Ischemia of the Spleen, *M. J. Tsapogas,* M.D., *R. A. Peabody,* PH.D., *A. M. Karmody,* M.B., CH.M., *C. Chuntrasakul,* M.D., *H. Goussous,* M.D., *C. Eckert,* M.D., Albany, New York

186 High Abdominal Aortic Aneurysm, Hepatic Artery Aneurysm, and Cystadenoma of Pancreas Treated Surgically in a Young Woman, *Benjamin F. Gibbs, Jr.,* M.D., *David R. James,* CDR., MC, USN, *Gary D. Ketron,* LCDR., MC, USNR, *Roger F. Milnes,* CAPT., MC, USN., San Diego, California

DYONICS GIVES YOU A SINGLE LIGHT GUIDE THAT ADAPTS TO ALL FIBER OPTIC INSTRUMENTATION



ACMI ADAPTOR

DYONICS ADAPTOR

WOLF ADAPTOR

JACKSON ADAPTOR

MPC ADAPTOR

PLASTIC AUTOCLAVE CANISTER

A Pilling-type light source tip and a comprehensive selection of fiber optic instrument couplings establish the Dyonics Light Guide as the most widely adaptable bundle available. The interchangeable couplings automatically reduce inventory requirements by allowing one fiber optic bundle to supply high intensity, "cool light" to the widest possible range of instrumentation.

Dyonics Light Guide fibers are enclosed in a non-conductive silicone sheath that permits maximum flexibility and repeated autoclaving. Wrapped stainless steel casings guard the flexible glass fibers at their ends where fractures most likely occur during use. Each light guide is shipped in a clear, plastic canister for protection during sterilization, handling and storage.

RICHARDS MANUFACTURING COMPANY, INC.
1450 BROOKS RD., MEMPHIS, TENN. 38116, A.C. 901 • 396-2121
IN CANADA, RICHARDS SURGICAL LIMITED, 130 EAST DRIVE, BRAMALEA, ONTARIO, L6T 1C3, (416) 677-9744

© RICHARDS MANUFACTURING CO., INC. 1973

PRINTED IN U.S.A.

CONTENTS *Continued*

190 Effect of Truncal, Selective and Highly Selective Vagotomy on Gastric Emptying and Intestinal Transit of a Food-Barium Meal in Man, *Alan R. Wilkinson,* MB, CHB, *David Johnston,* Leeds, Britain

194 Congenital Obstruction of the Pancreatic Duct at the Duodenum: A Report of Two Cases in Adulthood, *Thomas Taylor White, Helge Kavlie,* Seattle, Washington

197 Preoperative Endoscopic Cannulation of Pancreatic and Biliary Ducts, *Michael Kozower, Richard A. Norton, Robert E. Paul, Jr., Karim A. Fawaz, Harry H. Miller, Alan H. Robbins, Elihu M. Schimmel, Herman J. Sugarman, Jaime G. Tomas,* Boston, Massachusetts

200 Rupture of the Common Duct and Ampulla of Vater Due to Blunt Trauma, *Nicholas A. Balsano,* M.D., *Benedict M. Reynolds,* M.D., Bronx, New York

204 Effects of Parietal Cell Vagotomy on Acid and Pepsin Secretion in Gastric Fistula Dogs, *Ari Kaynan,* M.D., *Gur Ben-Ari,* M.D., *Allan E. Kark,* M.D., *Jack Rudick,* M.D., New York City

209 Portal Decompression: Clinical Experience with the "H" Graft, *Joseph L. Graziano,* M.D., *Henry J. Sullivan,* M.D., Hines, Illinois

215 Weight Loss Following Thermal Injury, *Thomas W. Newsome,* M.D., MAJOR, MC, *Arthur D. Mason, Jr.,* M.D., *Basil A. Pruitt, Jr.,* M.D., COL, MC, Fort Sam Houston, Texas

218 Systemic and Pulmonary Hemodynamic Changes Accompanying Thermal Injury, *Morris J. Asch,* M.D., LT COL, MC, *Richard J. Feldman,* CAPT, VC, *Harrel L. Walker,* M.S., *F. D Foley,* M.D., *Richard L. Popp,* M.D., MAJOR, MC, *Arthur D. Mason, Jr.,* M.D., *Basil A. Pruitt, Jr.,* M.D., COL, MC, Fort Sam Houston, Texas

222 Sepsis: A Mechanism for Vasodilatation in the Kidney, *Fredrick Rector,* M.D., *Suresh Goyal,* M.D., *Irwin K. Rosenberg,* M.D., *Charles E. Lucas,* M.D., Detroit, Michigan

When Pain
Cries for Relief!

Start oral DILAUDID (hydromorphone) 2 to 4 mg. every four hours . . . to alleviate moderate to severe pain . . . well tolerated . . . minimal sedation

CONTRAINDICATIONS: Intracranial lesions associated with increased intracranial pressure, status asthmaticus. WARNINGS: May be habit forming. If given intravenously, injection should be given very slowly. PRECAUTIONS: Usual precautions for administration of opiate analgesics should be observed; the possibility of respiratory depression should be kept in mind. If significant respiratory depression should occur, it may be antagonized by the use of nalorphine hydrochloride or levallorphan tartrate. ADVERSE REACTIONS: Nausea, vomiting, dizziness, somnolence, anorexia and constipation may occur. Rapid intravenous injection increases the possibility of hypotension and respiratory depression. HOW SUPPLIED: Tablets — 1 mg., 2 mg., 3 mg., 4 mg. Rectal Suppositories — 3 mg. in cocoa butter base. Ampules — 1 ml., 1 mg., 2 mg., 3 mg., and 4 mg. per ml. with 0.2% sodium citrate, 0.2% citric acid solution. Cough Syrup — 1 mg. Dilaudid hydrochloride and 100 mg. glyceryl guaiacolate per 5 ml.

A Schedule II (Ⓒ) narcotic. Requires Federal BND order form.

Dilaudid®
(hydromorphone)

KNOLL PHARMACEUTICAL COMPANY · WHIPPANY, NEW JERSEY 07981
· TORONTO, CANADA

Notice to Contributors and Subscribers

The ANNALS OF SURGERY considers for publication original articles only, papers which offer significant contributions to the advancement of surgical knowledge.

CONTRIBUTIONS. Original typed manuscripts and illustrations, plus three copies and 3 sets of illustrations, exchanges and book reviews should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY:

Jonathan E. Rhoads, M.D.
1000 Ravdin Institute, 3400 Spruce St.
Philadelphia, Pa. 19104

Manuscripts, as well as list of references, should be typed double spaced on one side of the paper, leaving wide margins. While every effort will be made to guard against loss, it is advised that authors retain copies of manuscripts submitted. The complete address for reprint requests should be included in the title page. All pages should be numbered.

Digits one to ten should be spelled out, except when used for units of measurement (time, weight, volume, dosage, degrees) percentage, or when decimals are involved; for numbers above ten, numerals should be used. Dorland's Medical Dictionary and Webster's International Dictionary may be used as standard references. Scientific names for drugs should be used when possible. Copyright or trade names of drugs should be capitalized. Units of measurement, *e.g.,* dosage, should be expressed in the metric system. Temperature should be expressed in degrees centigrade. Contributions in a foreign language, when accepted, will be translated and published in English.

Black and white illustrations will be reproduced free of charge, but the publisher reserves the right to establish a reasonable limit upon the number supplied. Colored illustrations will be published at the author's expense. Black and white photographs should be in the form of glossy prints. Line and wash drawings should be black on white paper, with lettering in black india ink, large enough to be readable after necessary reduction. Large or bulky illustrations should be accompanied by smaller glossy reproductions of the same, to facilitate their circulation among the reviewing members of the editorial board. Illustrations should be numbered, the tops indicated, and the author's name and the title of the article in brief appear on the back. A separate typewritten sheet of legends for the illustrations should be supplied.

A bibliography of numbered references in alphabetical order should appear at the end of the manuscript with corresponding numbering in the text. Bibliographies should conform to the style of the Index Medicus with the exception that the last page number should be omitted, viz: author's name, title of article, name of journal, volume number, first page number, and year of publication in the order named.

PUBLISHER'S NOTICES

CHANGE OF ADDRESS: Please allow 60 days before date of issue for change of address. Notification should include the old as well as the new address, with indication of whether the change is temporary or permanent. Please give the name of the journal.

Copies will not be replaced without charge unless we receive a request within 60 days of the mailing in the U. S. or within 90 days in all other countries.

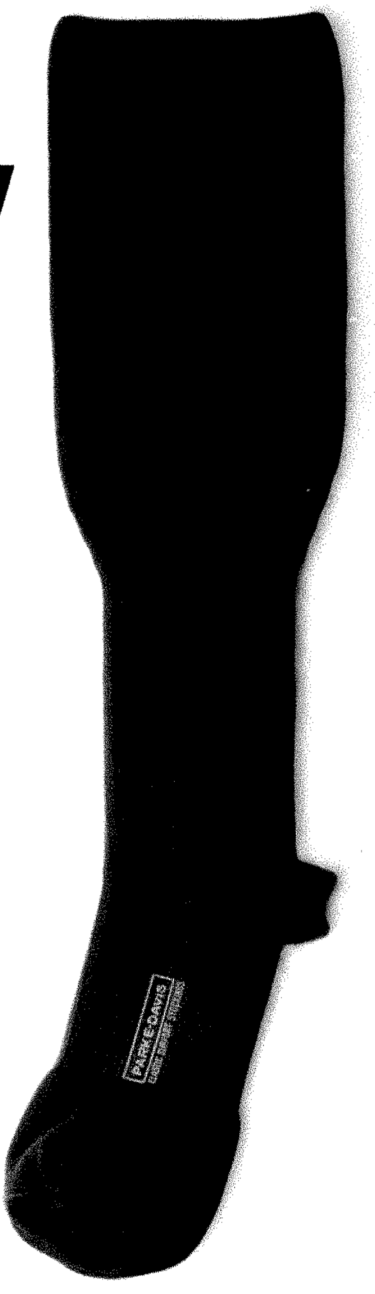
BUSINESS ADDRESS: Subscriptions, reprints, advertising, and all business communications should be addressed to:

ANNALS OF SURGERY
J. B. Lippincott Co.
East Washington Square
Philadelphia, Pa. 19105

Published Monthly. Subscription Rates $20.00 per year in the U. S., its possessions and Canada. All other countries $23.00. All prices include postage. Single issues $3.00. Rate for Residents, U. S. only, $14.00.

The publishers accept no responsibility for opinions expressed by contributors.

Our support hosiery looks funny for some very serious reasons.



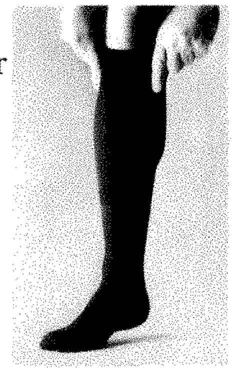
Compare Parke-Davis Elastic Support Hosiery with another brand—one you may now be recommending. See for yourself why ours best provides these important advantages.

1. *True, controlled graduated compression* means greater support at the foot and ankle, and gradually less support higher up the leg. Ours obviously provides this feature.

2. *Two-way stretch* is woven into the hosiery from bottom to top. So there's no need for a tourniquet-like band at the top to help keep the hosiery up. Ours obviously provides this feature.

3. *Medically-correct design* matches the needs of the patient with vascular disease of the lower extremities. Ours obviously provides this feature.

Result: our support hosiery does what support hosiery should do. It helps prevent edema. Minimizes venous pooling of blood. Helps reduce the leg pain associated with varicosities.



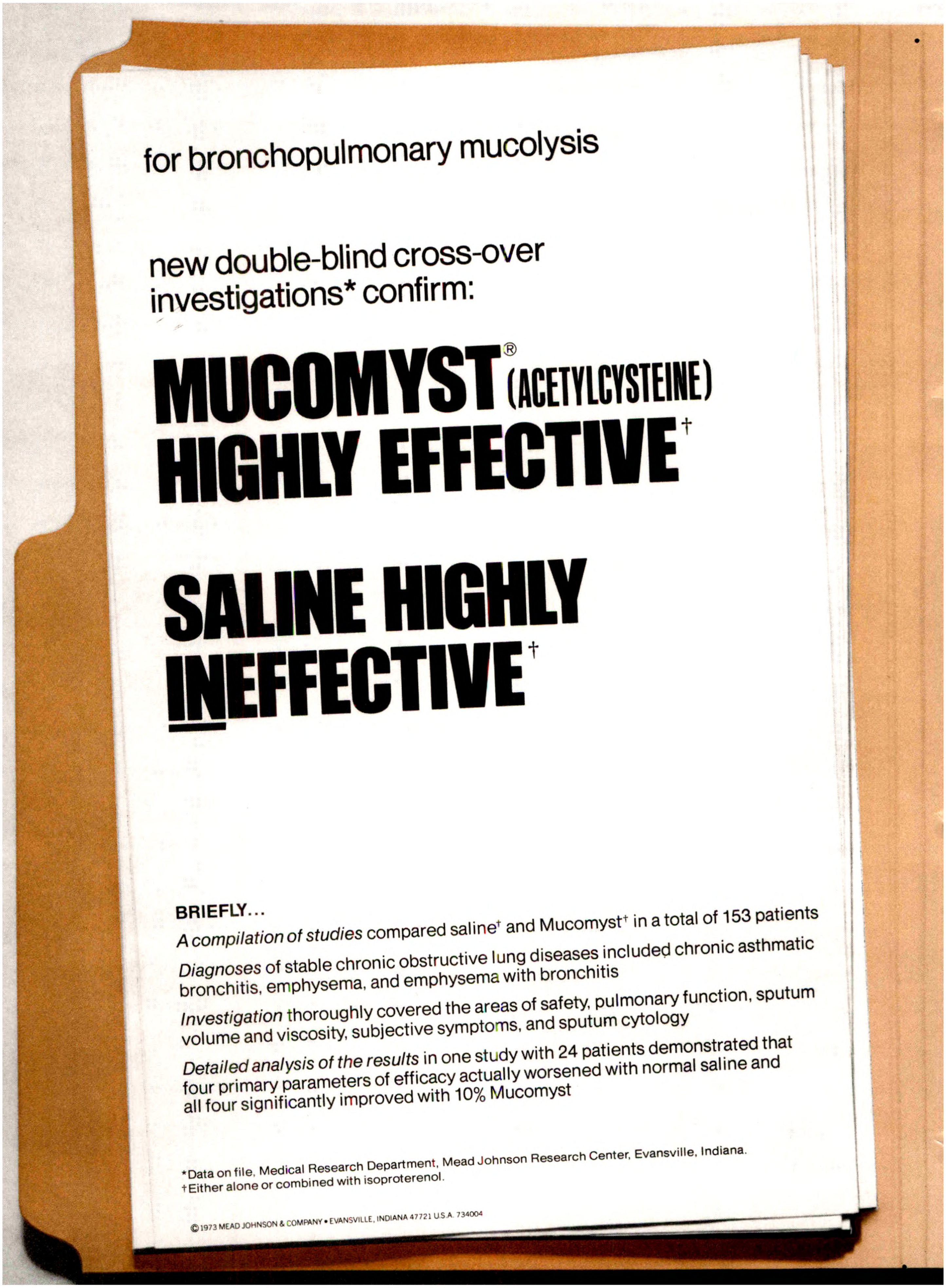
Incidentally, Parke-Davis Elastic Support Hosiery is made for women, too. Panty hose included. A complete range of sizes and sheerness. Better looking than men's hosiery—but still medically correct.

Seriously, isn't that beautiful?

PARKE-DAVIS
ELASTIC SUPPORT HOSIERY

They look funny–
until you
put them on.

Parke, Davis & Company • Detroit, Michigan 48232
PD-JA-0996-1-C (2-73)



for bronchopulmonary mucolysis

new double-blind cross-over
investigations* confirm:

MUCOMYST® (ACETYLCYSTEINE) HIGHLY EFFECTIVE†

SALINE HIGHLY INEFFECTIVE†

BRIEFLY...

A compilation of studies compared saline† and Mucomyst† in a total of 153 patients

Diagnoses of stable chronic obstructive lung diseases included chronic asthmatic bronchitis, emphysema, and emphysema with bronchitis

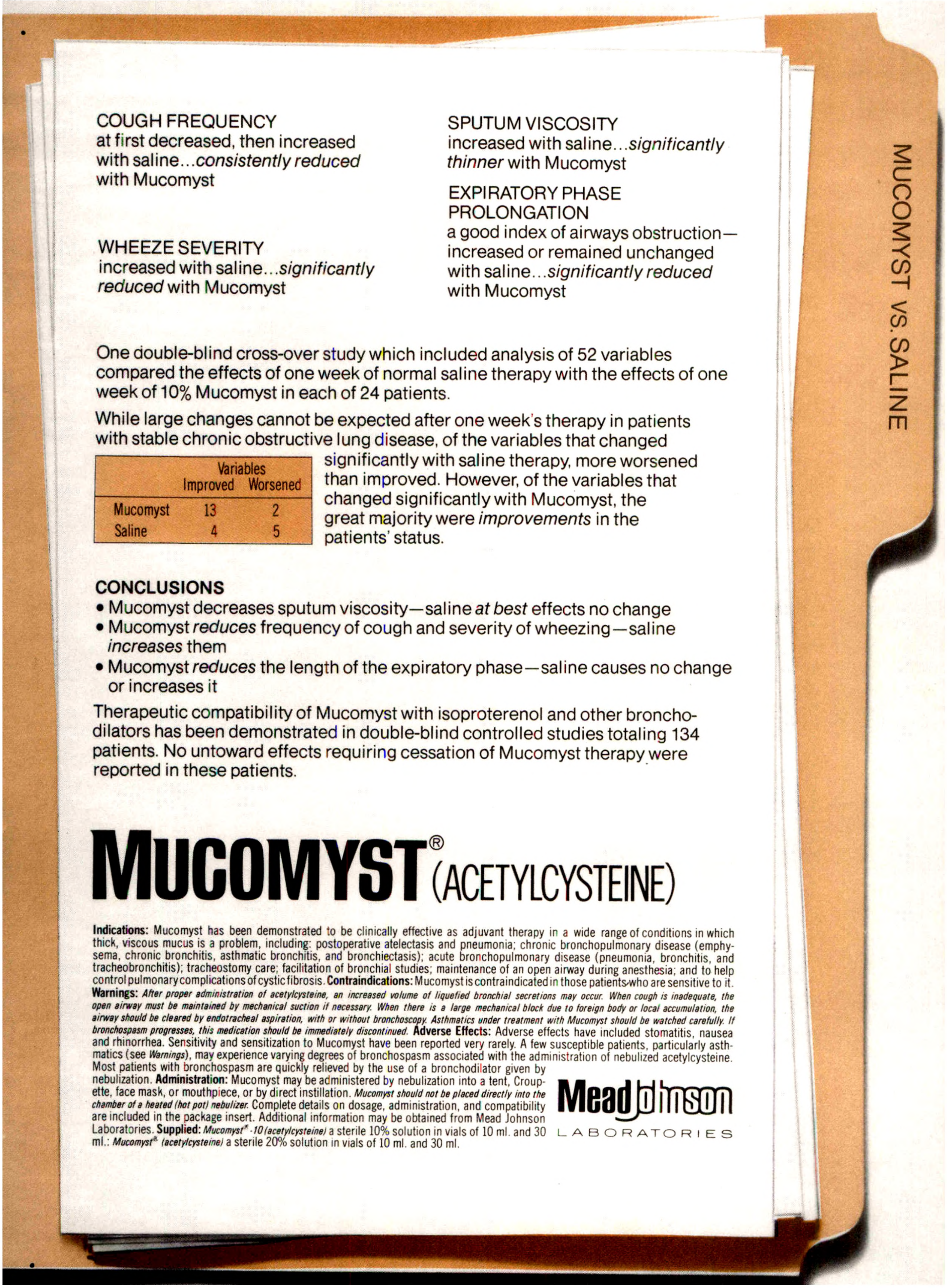
Investigation thoroughly covered the areas of safety, pulmonary function, sputum volume and viscosity, subjective symptoms, and sputum cytology

Detailed analysis of the results in one study with 24 patients demonstrated that four primary parameters of efficacy actually worsened with normal saline and all four significantly improved with 10% Mucomyst

---

*Data on file, Medical Research Department, Mead Johnson Research Center, Evansville, Indiana.
†Either alone or combined with isoproterenol.

© 1973 MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA 47721 U.S.A. 734004



COUGH FREQUENCY
at first decreased, then increased with saline...*consistently reduced* with Mucomyst

WHEEZE SEVERITY
increased with saline...*significantly reduced* with Mucomyst

SPUTUM VISCOSITY
increased with saline...*significantly thinner* with Mucomyst

EXPIRATORY PHASE PROLONGATION
a good index of airways obstruction—increased or remained unchanged with saline...*significantly reduced* with Mucomyst

One double-blind cross-over study which included analysis of 52 variables compared the effects of one week of normal saline therapy with the effects of one week of 10% Mucomyst in each of 24 patients.

While large changes cannot be expected after one week's therapy in patients with stable chronic obstructive lung disease, of the variables that changed significantly with saline therapy, more worsened than improved. However, of the variables that changed significantly with Mucomyst, the great majority were *improvements* in the patients' status.

	Variables	
	Improved	Worsened
Mucomyst	13	2
Saline	4	5

CONCLUSIONS
- Mucomyst decreases sputum viscosity—saline *at best* effects no change
- Mucomyst *reduces* frequency of cough and severity of wheezing—saline *increases* them
- Mucomyst *reduces* the length of the expiratory phase—saline causes no change or increases it

Therapeutic compatibility of Mucomyst with isoproterenol and other bronchodilators has been demonstrated in double-blind controlled studies totaling 134 patients. No untoward effects requiring cessation of Mucomyst therapy were reported in these patients.

MUCOMYST® (ACETYLCYSTEINE)

Indications: Mucomyst has been demonstrated to be clinically effective as adjuvant therapy in a wide range of conditions in which thick, viscous mucus is a problem, including: postoperative atelectasis and pneumonia; chronic bronchopulmonary disease (emphysema, chronic bronchitis, asthmatic bronchitis, and bronchiectasis); acute bronchopulmonary disease (pneumonia, bronchitis, and tracheobronchitis); tracheostomy care; facilitation of bronchial studies; maintenance of an open airway during anesthesia; and to help control pulmonary complications of cystic fibrosis. **Contraindications:** Mucomyst is contraindicated in those patients who are sensitive to it. **Warnings:** *After proper administration of acetylcysteine, an increased volume of liquefied bronchial secretions may occur. When cough is inadequate, the open airway must be maintained by mechanical suction if necessary. When there is a large mechanical block due to foreign body or local accumulation, the airway should be cleared by endotracheal aspiration, with or without bronchoscopy. Asthmatics under treatment with Mucomyst should be watched carefully. If bronchospasm progresses, this medication should be immediately discontinued.* **Adverse Effects:** Adverse effects have included stomatitis, nausea and rhinorrhea. Sensitivity and sensitization to Mucomyst have been reported very rarely. A few susceptible patients, particularly asthmatics (see *Warnings*), may experience varying degrees of bronchospasm associated with the administration of nebulized acetylcysteine. Most patients with bronchospasm are quickly relieved by the use of a bronchodilator given by nebulization. **Administration:** Mucomyst may be administered by nebulization into a tent, Croupette, face mask, or mouthpiece, or by direct instillation. *Mucomyst should not be placed directly into the chamber of a heated (hot pot) nebulizer.* Complete details on dosage, administration, and compatibility are included in the package insert. Additional information may be obtained from Mead Johnson Laboratories. **Supplied:** *Mucomyst®-10 (acetylcysteine)* a sterile 10% solution in vials of 10 ml. and 30 ml.: *Mucomyst® (acetylcysteine)* a sterile 20% solution in vials of 10 ml. and 30 ml.

Mead Johnson
LABORATORIES

With the Seamless Dual-Finish™ Surgeons' Glove, the end of powder granuloma could be at hand.

To make it easy to don, a surgeons' glove has to be powdered. Unfortunately, however, it's a practice that can lead to powder granuloma.

What we've done in coming up with our disposable Seamless Dual-Finish™ Surgeons' Glove, is create a glove with an external surface to which powder won't adhere. The result is a glove that's easy to don, and just about certain not to contaminate the operative field!

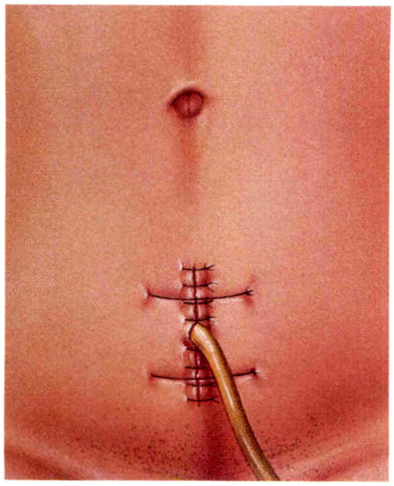
And as if that weren't enough, the Dual-Finish is made on a newly designed mold to offer unsurpassed comfort, sensitivity and fit.

Let us help you evaluate the Seamless Dual-Finish Surgeons' Glove with an in-hospital test. Once you see the results we think you'll agree it's the ultimate glove to have on hand! For aid in conducting an evaluation test talk to your Seamless representative or write direct to Seamless, New Haven, Conn. 06503.

seamless

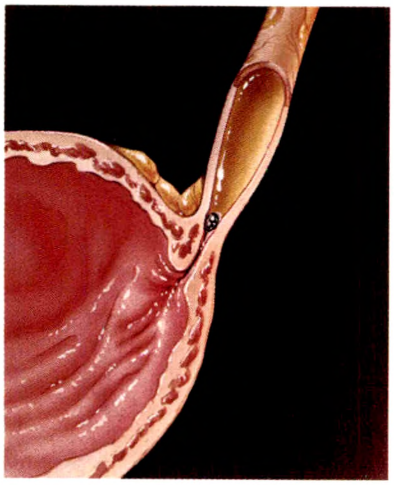
WHEREVER IT HURTS

HERE After surgery



Wherever it hurts, Empirin Compound with Codeine usually provides the relief needed.

HERE Renal calculus



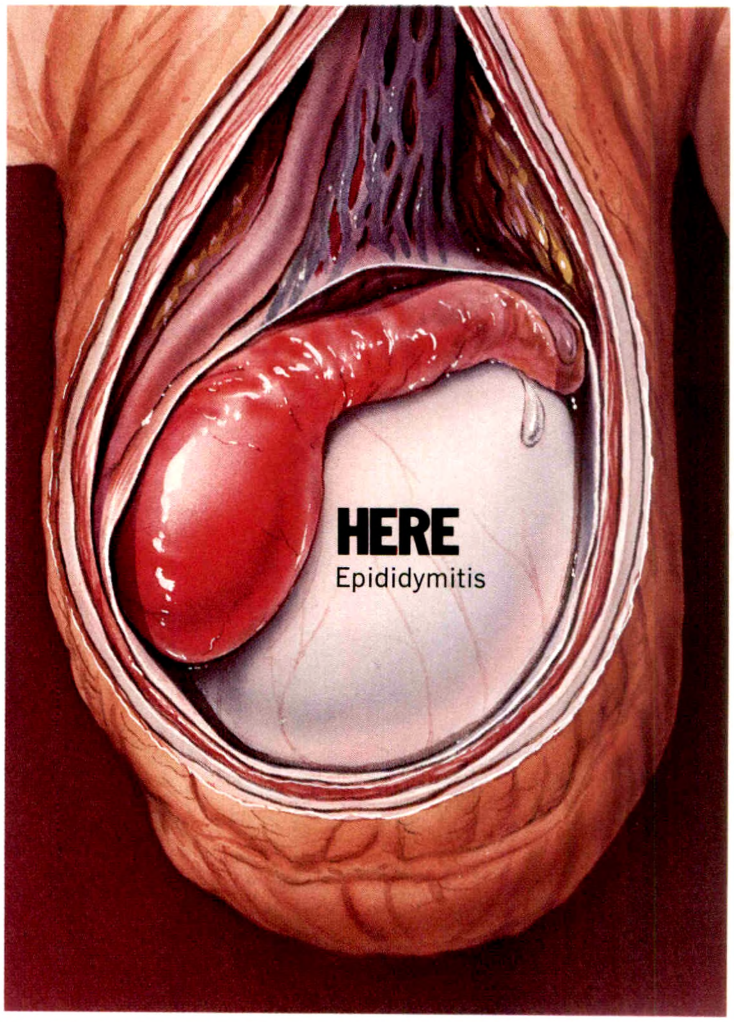
In general, only pain so severe that it requires morphine is beyond the scope of Empirin Compound with Codeine.

Ⓒ III **prescribing convenience:** up to 5 refills in 6 months, at your discretion (unless restricted by state law); by telephone order in many states.

Empirin Compound with Codeine **No. 3**, codeine phosphate* 32.4 mg. (gr. ½); **No. 4**, codeine phosphate* 64.8 mg. (gr. 1). *Warning—may be habit-forming. Each tablet also contains: aspirin gr. 3½, phenacetin gr. 2½, caffeine gr. ½.

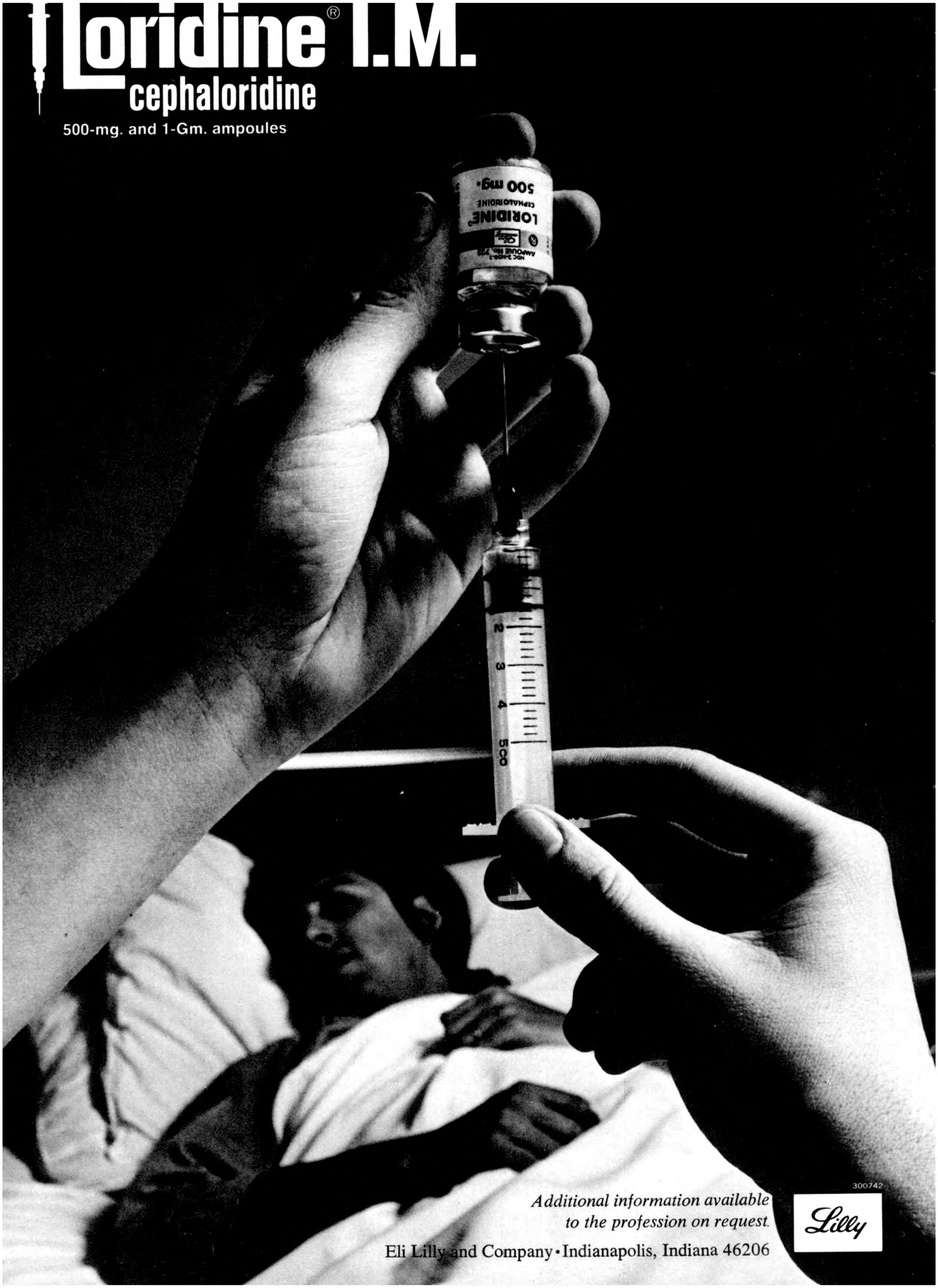
Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709



EMPIRIN® COMPOUND c̄ CODEINE

#3, codeine phosphate* (32.4 mg.), gr. ½
#4, codeine phosphate* (64.8 mg.), gr. 1



Loridine® I.M.
cephaloridine
500-mg. and 1-Gm. ampoules

Additional information available to the profession on request.

Eli Lilly and Company • Indianapolis, Indiana 46206

Lilly

300742

ANNALS OF SURGERY

Vol. 178 August 1973 No. 2

Sequential System Failure after Rupture of Abdominal Aortic Aneurysms:

An Unsolved Problem in Postoperative Care

NICHOLAS L. TILNEY, M.D.,[*] GEORGE L. BAILEY, M.D.,[**]
ALFRED P. MORGAN, M.D.[***]

From the Department of Surgery of Harvard Medical School at the Peter Bent Brigham Hospital, Boston, Massachusetts

CERTAIN COMBINATIONS of disease and trauma form lethal syndromes. Components of those syndromes, taken individually, can often be treated effectively, but when they occur together, therapy is unsuccessful. One of these combinations is acute renal failure and the otherwise successful surgical treatment of a ruptured aortic aneurysm. An example of particular interest, it is a worse-case challenge to present-day technics of postoperative care.

The mortality of ruptured abdominal aneurysm alone is 32%–85% for patients who live to reach the operating room. Some of these deaths occur during the operative and early postoperative periods in those individuals who are not completely resuscitated. Others go on to a phase of apparent stability. At this time, typically the first or second postoperative day, blood volume has been restored and hemostasis accomplished. The patient may have good cerebral and cardiovascular function and breathe spontaneously without assistance. Most patients reaching this point will survive, though subject to the ordinary vicissitudes of recovery from major operation. For one sub-group, those with fixed renal failure, survival is exceptional.

Alone, the mortality of uncomplicated renal failure is small, approaching the risk of chronic hemodialysis. This has been reported as only 3% when the underlying condition is "slight or cured."[1] The hazard of ruptured abdominal aortic aneurysm, and acute renal failure together is greater than the sum of their risks taken singly. Almost all patients subjected to this combination will experience progressive, sequential, organ system failure and eventually succumb. Our experience with patients in this category is reported to demonstrate the need for a more effective approach to their therapy, and in its absence, as an aid to judgment in the difficult balancing of expenditure of medical resources against probable gain to the patient.

Clinical Material

Patient Selection

This series includes all patients treated by hemodialysis for postoperative acute renal failure after rupture of an abdominal aneurysm during the past 15 years.

Submitted for publication October 6, 1972.

Supported in part by grants from the John A. Hartford Foundation, Inc., the National Institutes of Health, and the Research and Development Command of the United States Army.

[*] Senior Resident in Surgery, Peter Bent Brigham Hospital.

[**] Instructor in Medicine, Harvard Medical School and Peter Bent Brigham Hospital; Chief, Home Dialysis Service.

[***] Assistant Professor of Surgery, Harvard Medical School; Associate in Surgery, Peter Bent Brigham Hospital.

Request reprints: Alfred P. Morgan, M.D., 721 Huntington Avenue, Boston, Massachusetts 02115.

TABLE 1. *Occurrence of Unfavorable Prognostic Factors in 18 Patients with Acute Renal Failure after Ruptured Abdominal Aneurysm*

	Number	Per Cent
Pre-existing Systemic Disease		
Chronic pulmonary insufficiency	9	50%
Heart disease	14	78
Infarct by history or EKG	11	
Congestive failure	2	
Arrhythmia	1	
Hypertension	10	56
Obesity	6	33
Intraoperative events		
Hypotension (<80 mm. Hg)	16	80
Cardiac arrest	4	22

Patients who did not survive for 5 postoperative days were excluded to eliminate those for whom operative resuscitation was unsuccessful. Clinical information has been taken from hospital and intensive care records; the authors participated in the care of the majority.

Composition of the Series

Eighteen patients meeting this description were found in the records of the Peter Bent Brigham Hospital for the 15-year period ending January 1, 1971. Only one patient survived. Fifteen (84%) were men, and three were (16%) women. Mean age of men was 63 years, of women 76 years. Five patients had been transferred postoperatively from other hospitals. For the majority, a number of factors correlating with increased risk were recognized preoperatively or occurred during operation. As shown in Table 1, 16 patients were hypotensive (systolic pressure less than 80 mm. Hg at some time). Cardiac arrest occurred during operation in four and a thoracotomy was performed in three of these patients. Ten patients underwent a second operative procedure of some sort at some time, exclusive of arteriovenous shunt insertion (Table 2). Seventeen patients died; the mortality thus exceeded 90%. The mean time to death was 18 postoperative days (range 5-48).

Analysis of Data

The objective in reviewing the clinical record was to learn at what time during the course, failure of an organ or organ system was first observed. Evidence was obtained from records of laboratory data, bedside observation, or the initiation of therapy in support of a particular system. Criteria defining failure were necessarily specific to the organ or system. For the pancreas it was serum amylase levels twice normal (beyond the expected renal failure range). Pulmonary failure was defined as need for mechanical ventilation. Liver failure was defined as observation of clinical jaundice (or serum bilirubin greater than 3 mg./100 ml.). Failure of the central nervous system (CNS) was defined as failure to respond to other than painful stimuli. Failure of the gastrointestinal tract was equated to bleeding that required transfusion. Gross blood from the nasogastric tube distinguished failure of the upper GI tract, bright red blood from the rectum signified failure of the lower tract. Cardiac failure was established either by hypotension with elevated right atrial pressure, an arrhythmia compromising cardiac output, or electrocardiographic evidence of myocardial infarction.

TABLE 2. *Surgical Procedures after Aneurysmectomy*

Procedure	Number
Femoral Embolectomy	4
Laparotomy for Bleeding	2
Femoral Vein Ligation	1
Pyloroplasty, Vagotomy	1
Sigmoid Resection	1
Insertion of Pacemaker	1
Tracheostomy	12
Arteriovenous Shunt	18

An effort was also made to assign an immediate cause of death by combining data from autopsy and clinical records. Though subject to judgment, for most of the patients this determination was made without difficulty.

Treatment

A maximum and concentrated therapeutic effort was made for every patient. Details of management varied over the period covered by the review. Antibiotic agents of increased effectiveness became available during this time (but have been matched by an increased frequency of significant infection by previously commensal organisms). Pressure cycled ventilators were replaced by volume limited machines. The incidence of tracheostomy decreased, and the use of arterial and central venous monitoring catheters became universal. The principles underlying use of dialysis have been little changed. They are early and frequent hemodialysis (4–6 hours every second day; maximum flow consistent with hemodynamic stability). Recently, the use of parenteral nutrition has slowed the rate of increase of blood urea and potassium concentration during intervals between dialyses, but the same treatment schedule is maintained in order to palliate the other components of the uremic syndrome: CNS depression, interference with wound healing, and increased susceptibility to infection.

Results

Although 17 of the 18 patients died, there was a wide distribution of survival times. One died on the 5th postoperative day, one on the 48th; the remaining 15 deaths occurred between these extremes. Despite these differences, a similar progression of organ system failure was observed in all. The sequence unfolded more slowly in patients who survived longer, and developed quickly in those surviving for shorter periods, but most patients developed all components of the pattern in approximately the same order before death occurred. This is shown in Figure 1 where the onset of organ system failure for all patients is compared on a common time scale. There was some variation from patient to patient in the manner of presentation and pathophysiology of specific organ system failure, as follows.

Central Nervous System

Some form of major neurologic abnormality was recorded in all patients but one. The commonest was coma, occurring in 11. It was manifested by lack of response to all but painful stimuli or to tracheal stimulation but without localizing signs or primitive reflexes. Five patients experienced six episodes that were marked by focal neurologic findings; three occurred early and were probably caused by local ischemia or low-flow thrombosis during the shock period. Three episodes occurred terminally.

Lungs

Respiratory failure which occurred in all of these patients was the leading cause of death (Table 3). All patients who died required mechanical ventilation before death. Contributory causes to impairment of pulmonary function, such as hepatic failure, tended to follow a pattern of early appearance, apparent improvement, and then secondary progressive failure. Morphologic changes at autopsy were extensive and nonspecific. Lungs were heavy; microscopically there was bronchopneumonia, interstitial edema, alveolar hemorrhage and hyaline membrane formation. Organisms were grown from all postmortem cultures, *Pseudomonas* or *Escherichia coli* from the majority, a mixed group of Gram-negative enteric organisms from the remainder, but in only one patient was there major tissue reaction to infection. None had significant pulmonary emboli.

Heart

It is accepted that an arteriosclerotic abdominal aortic aneurysm is a late manifestation of generalized cardiovascular disease, attested to by the presence of an old, healed myocardial infarction in more than half of these patients and by occurrence of a new infarct during the postoperative period in three. All occurred during the second postoperative week. Four other patients experienced significant arrhythmias requiring treatment by cardioversion, pacemaker, or drugs. Autopsy showed extensive coronary artery disease in all patients; uremic pericarditis was found in two.

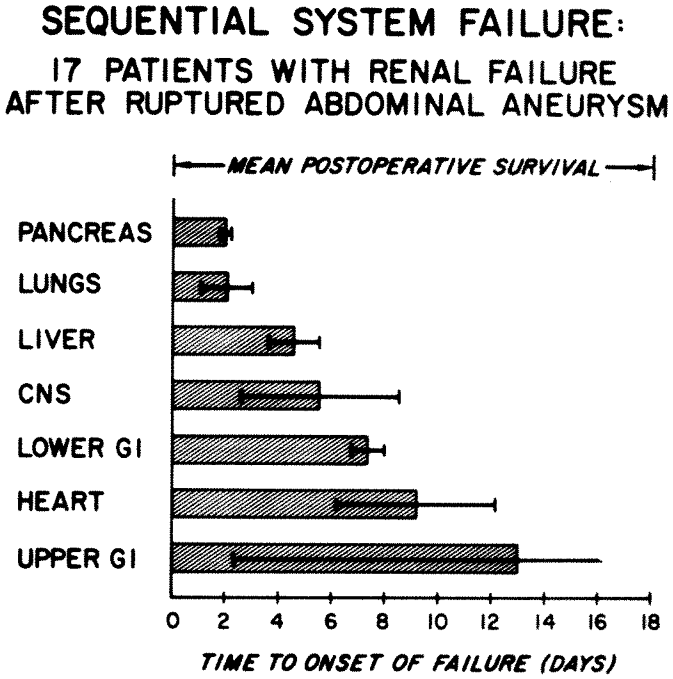


FIG. 1. The order of appearance of organ system failure is shown by normalizing survival time for each patient to mean duration of survival for the group.

Liver

All patients were jaundiced, chemically or clinically. Bilirubin and enzyme levels followed a characteristic pattern: early, transient elevation of hepatocellular enzymes, a later and more or less steady increase in bilirubin to very high levels (Fig. 2). Histologic changes were correspondingly severe—centrilobular necrosis, significant bile stasis, congestion and lipid infiltration. There was one instance of ductal obstruction by pancreatitis, one of multiple septic infarcts.

Pancreas

Fulminent pancreatitis was recognized early (on the second postoperative day) in two instances but could be seen retrospectively to have occurred in a total of nine patients, in whom severe pancreatitis was found at autopsy, and could be correlated with antemortem amylase elevation and a plasma requirement. Pan-

TABLE 3. *Proximate Causes of Death (17 Patients)*

	Primary	Secondary	Total
Respiratory Failure	9	4	13
Septicemia	3	7	10
Gastrointestinal Hemorrhage	1	1	2
Acute Pancreatitis	2	1	3
Cardiac Failure		2	2
Uremia		1	1
Multiple Factors	2	1	3

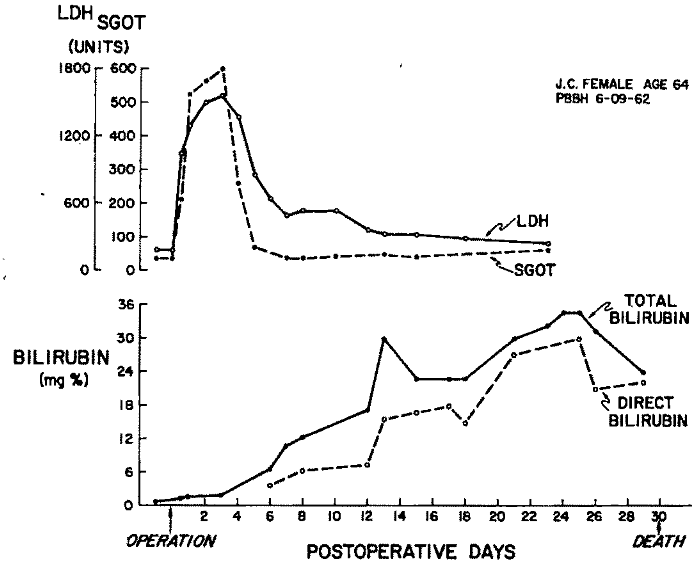


Fig. 2. The characteristic evolution of plasma enzyme and bilirubin levels as seen in one patient.

creatitis was hemorrhagic and necrotizing in four, in three there was inflammation, edema, and fat necrosis.

Gastrointestinal Tract

Gastrointestinal complications occurred late in these patients (Fig. 1) but were seen in all. Some complications were recognized prior to death: major upper gastrointestinal hemorrhage in eight patients (one died of recurrent bleeding after pyloroplasty and vagotomy); massive bleeding from the colon in two, sigmoid perforation in one. At autopsy previously unrecognized necrosis and perforation of the sigmoid was present in two patients, some degree of gastric erosion and ulceration was recognized in all.

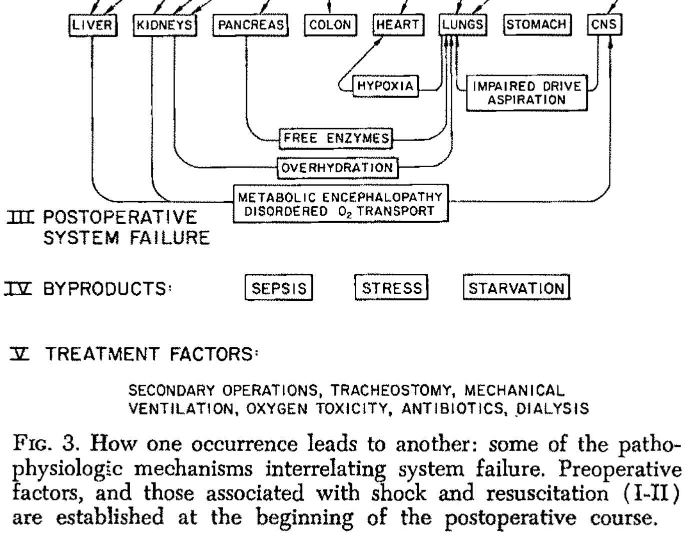

I PREOPERATIVE FACTORS:
AGE; OBESITY; PREEXISTING CARDIOVASCULAR, PULMONARY, RENAL DISEASE
HYPOTENSION LOW FLOW
II SHOCK AND RESUSCITATION:
VASOPRESSORS
ANESTHESIA
OPERATIVE TRAUMA
TRANSFUSION
CLAMP EMBOLI
LIVER
KIDNEYS
PANCREAS
COLON
HEART
LUNGS
STOMACH
CNS
HYPOXIA
IMPAIRED DRIVE ASPIRATION
FREE ENZYMES
OVERHYDRATION
METABOLIC ENCEPHALOPATHY DISORDERED O2 TRANSPORT
III POSTOPERATIVE SYSTEM FAILURE
IV BYPRODUCTS:
SEPSIS
STRESS
STARVATION
V TREATMENT FACTORS:
SECONDARY OPERATIONS, TRACHEOSTOMY, MECHANICAL VENTILATION, OXYGEN TOXICITY, ANTIBIOTICS, DIALYSIS

Fig. 3. How one occurrence leads to another: some of the pathophysiologic mechanisms interrelating system failure. Preoperative factors, and those associated with shock and resuscitation (I-II) are established at the beginning of the postoperative course.

Kidneys

Autopsy demonstrated bilateral acute tubular necrosis superimposed on varying degrees of nephrosclerosis in most of the patients. There were several exceptions: bilateral cortical necrosis in one patient, in two examinations cortical necrosis was found in one kidney, tubular necrosis in the other. One case emphasized a clinical principle, the importance of demonstrating bilateral patency of the ureters. A clear lower tract was shown by retrograde pyelography of the left kidney but the right ureteral orifice could not be intubated in this individual. Autopsy revealed renal infarction on the left, with ureteral ligation and hydronephrosis on the right.

Discussion

The question presented by these patients is familiar and fundamental: how do a number of physiologic liabilities, each in itself potentially reversible, combine to make survival exceptional, though not impossible; for even in this group there was one survivor. This individual did not differ from the others in age, preoperative cardiovascular status, or need for postoperative respiratory support.

There are established interrelationships between organ systems which help explain both the additional hazard created by renal failure, and the characteristic sequence of events during the postoperative course. Failure of one system challenges others and improvement in survival depends on identification of points where these cycles can be interrupted. Some of them are not controllable. For example, those existing preoperatively or occurring intraoperatively (Fig. 3) are difficult or impossible to modify. Many operative factors are common to survivors of hemorrhage, shock or trauma generally, a few are peculiar to aneurysmal resection. For example, aortic cross clamping may cause renovascular constriction, atheromatous embolism, parenchymatous arteriovenous shunting, and renal artery pressure changes.[3] Clamp release can initiate washout acidosis, increasing damage to already compromised renal tubules, and possibly allow a shower of microemboli to reach the lungs.[2] Direct operative trauma to the kidney or collecting system can occur, as it did in one patient in this series; similarly, operative trauma to the pancreas or the inferior mesenteric circulation may set the stage for problems later, and pancreatitis occurred frequently.

Respiratory failure, however, was the commonest proximate cause of death. Successful resuscitation from massive hemorrhage and management of the metabolic consequences of renal failure allows development of what has been variously called shock lung, post-traumatic pulmonary insufficiency, or progressive pulmonary insufficiency.[5] Less clearly related to operative events, its etiology is probably mixed and possibly unknown; a long list of factors which may share responsibility can be made. The principal difficulty in dealing with the syndrome of post-traumatic pulmonary insufficiency lies in assessment of the relative importance of these possible causative factors. Some are part of the resuscitation and hence unavoidable: microembolism after aortic cross clamping, previously mentioned, the load of embolic material imposed by many transfusions, and the pulmonary vascular response to hypovolemia and to vasopressors which may be used in its treatment. After resuscitation, the lungs remain the principal target of changes initiated by failure of other organs and of the undesirable effects of necessary therapy. Figure 3 shows some of these relationships, in a necessarily abbreviated way. Not all can be modified by present day methods but some can. Of those influencing the lung, for example, overhydration can be avoided or treated by early dialysis. All of these patients had received large quantities of water and sodium for initial replacement of lost intravascular volume, intraoperative extracellular fluid expansion, and as a trial of volume loading when oliguria was first noted. Large positive water balances could be calculated at the time of admission to the intensive care unit. Simply restricting water leads to hypertonicity unless gastrointestinal losses are large: combining some water restriction with hemodialysis (massive water removal by ultra-filtration may not be tolerated hemodynamically) improves the chest X-ray and alveolar-arterial gradient for oxygen, but avoiding the early phase of hyperhydration might be an advance. Good principles of respiratory management are certainly important, but obviously not the whole answer, and need not be detailed here. Maintenance of nutrition parenterally may be important, at least to maintain respiratory muscle function and possibly in more indirect ways.

Gastric mucosal ulceration, like postoperative pulmonary insufficiency, is a standard surgical topic. Recent reports emphasize the importance of gastric resection in its treatment, and this series includes a patient who rebled after pyloroplasty and vagotomy. Other than this there was little to learn except that episodes of bleeding usually occurred in association with hemodialysis, even when regional heparinization was tightly controlled, and that massive upper GI bleeding was a late event, which in a setting of multiple organ system failure might have been interpreted as marking the point at which vigorous therapy should be discontinued.

Renal failure, once clearly established, is unlikely to resolve before hemodialysis is required. These patients have additional loading of potassium and nitrogen metabolites from hematoma and devitalized tissue even where hypercatabolic nutritional requirements are met parenterally. The objectives are to keep serum potassium within the normal range, avoid central depression, and to maintain dry lungs. The effect of intensive dialysis on wound healing has been established in man and animal[6,7]; there is also evidence from animal studies that dialysis can partially reverse the effects of uremia on leucocyte function, the gastrointestinal epithelium, and hematopoiesis.

The universal occurrence of profound increasing jaundice was a distinguishing feature. Explanations are available: a large pigment load from transfusions and hematoma with no renal clearance of plasma bilirubin; splanchnic vasoconstriction in hypovolemic shock profound enough to cause acute renal failure also results in hepatocellular damage.[6] In patients in whom acute renal failure followed operations other than aneurysm resection, where survival is more frequent, bilirubin levels often continued to be elevated for weeks after diuresis and return of BUN and creatine to normal levels.

Diagnoses were missed despite close observation and frequent re-evaluation; most often they were intraabdominal complications: *e.g.*, pancreatitis and sigmoid perforation. The treatment of pancreatitis presents few surgical options, although its frequency in this series illustrates the truth that not all amylase elevation in acute renal failure is due to impaired clearance. Ischemic necrosis and perforation of the sigmoid colon after aneurysm resection, such as massive bleeding from stress ulcers, carries an extremely high mortality.[4] Again, this event might in the whole setting of the patient's preoperative state of health, family wishes, and available resources allow some judgment to be made concerning the wisdom of further treatment.

Summary

Eighteen patients required hemodialysis after surgical treatment of ruptured abdominal aortic aneurysm. Review of the clinical events and autopsy findings showed a similar progression of organ system failure, beginning with pancreatic to pulmonary disease, and progressing to upper GI bleeding. A significant incidence of clinically silent (or at least undetected) major intraperitoneal disease was also noted. The lethality of renal failure after ruptured aneurysm is explained as a superimposition of pre-existing chronic cardiovascular disease

on the mechanical and metabolic consequences of the surgical procedure. Even though some of the mechanisms are well understood, their combination initiates a cycle which is difficult to interpret: mortality for this group of patients was greater than 90%.

References

1. Balslov, J. T. and Jorgensen, H. E.: A Survey of 499 Patients with Acute Anuric Renal Insufficiency. Am. J. Med., 34:753, 1963.
2. Blaisdel, F. W., Lim, R. C., Jr., and Stallone, R. J.: The Mechanism of Pulmonary Damage Following Traumatic Shock. Surg. Gynecol. Obstet., 130:15, 1970.
3. Christiansen, J. and Mouridsen, H. T.: Ruptured Aneurysm of the Abdominal Aorta. Acta. Chir. Scand., 133:111, 1967.
4. Kantrowitz, P. A., Jones, W. A., Greenberger, N. J., Isselbacher, K. J.: Severe Postoperative Hyperbilirubinemia Simulating Obstructive Jaundice. N. Engl. J. Med., 276:591, 1967.
5. Moore, F. D., Lyons, J. H., Jr., Pierce, E. C., Jr., Morgan, A. P., Drinker, P. A., MacArthur, J. D., and Dammin, G. J.: Post-Traumatic Pulmonary Insufficiency. W. B. Saunders Co., 1969.
6. Nayman, J.: Effect of Renal Failure on Wound Healing in Dogs. Response to Hemodialysis Following Uremia Induced by Uranium Nitrate. Ann. Surg., 164:227, 1966.
7. Schreiner, G. E. and Maher, J. F.: The Patient with Chronic Renal Failure and Surgery. Am. J. Cardiol., 12:31, 1963.

Hemodynamics of Innominate Artery Occlusion

DAVID J. MOZERSKY M.D.,* ROBERT W. BARNES M.D.,**
DAVID S. SUMNER M.D.,*** D. EUGENE STRANDNESS JR., M.D.†

Since the initial description of reversed flow in the vertebral artery by Contorni[2] many reports have appeared in which similar flow patterns have been described. The name *subclavian steal syndrome* was proposed by the editors of the *New England Journal of Medicine*[3] to denote patients with this hemodynamic lesion and associated neurologic findings. Although the great majority of these cases result from occlusions of the subclavian artery, occlusions of the innominate artery may also produce a variant of this defect. These two lesions differ significantly from both the hemodynamic and clinical viewpoints. When innominate stenosis is present not only is the vertebral flow reversed but also the blood flow in the right carotid artery is reduced and its direction may even be changed.

In most reports describing the physiology of innominate artery occlusion, radiographic technics have been used to evaluate the alterations in blood flow. The development of the directional ultrasonic velocity detector has provided a method by which flow direction and relative magnitude can be estimated transcutaneously. This instrument facilitates the evaluation of flow at rest and under the influence of physiologic stimuli.

The present report outlines the hemodynamic defect in patients with innominate artery occlusion and illustrates the usefulness of the directional ultrasonic velocity detector in the study of the problem.

From the Department of Surgery, University of Washington and the Veterans Administration Hospital, Seattle, Washington

Material and Methods

The directional ultrasonic velocity detector has been used to evaluate blood flow in three patients who presented with reduced systolic pressures in the right arm. Initially, flow tracings from right and left brachial, carotid and vertebral arteries were obtained transcutaneously. By these techniques both the contour of the flow pulse and its direction, could be determined. A blood pressure cuff was then placed around the right arm and inflated to pressures above systolic pressure for three minutes. Flow recordings from the carotid and vertebral vessels were obtained during the time the cuff was rapidly deflated. In this way, the effect of hyperemia of the arm on carotid and vertebral flow could be evaluated.

Case Reports

Case 1. A 53-year-old mentally retarded man was well until 2 weeks prior to admission, when he lost the ability to walk without support. The event occurred suddenly and persisted unchanged from the time of onset until his admission. In addition to this symptom he had noted decreased sensation and numbness in the right hand. The remainder of the history was not contributory. Physical examination revealed a diminished pulse and pulse delay in the right brachial artery. The systolic pressure was 154 mm. Hg in his left arm and 110 mm. Hg in the right. No pulse was palpable in the right carotid artery. A right carotid bruit was present. Although generalized motor weakness was observed, no localizing signs were noted.

The patient was referred to the peripheral vascular laboratory for flow studies with the directional ultrasonic velocity detector. Abnormal flow patterns were observed in the right brachial (Fig. 1) and carotid arteries. Reversal of flow in the right vertebral artery was also noted. When hyperemia was induced in the right

---

Submitted for publication June 6, 1972.
Supported by USPHS grant HL 05921.

* Surgeon, Wilford Hall, USAF Medical Center.

** Assistant Professor of Surgery, University of Iowa.

*** Associate Professor of Surgery, University of Washington, Clinical Investigator, Seattle Veterans Administration Hospital.

† Professor of Surgery.

Reprint request to Dr. Sumner.

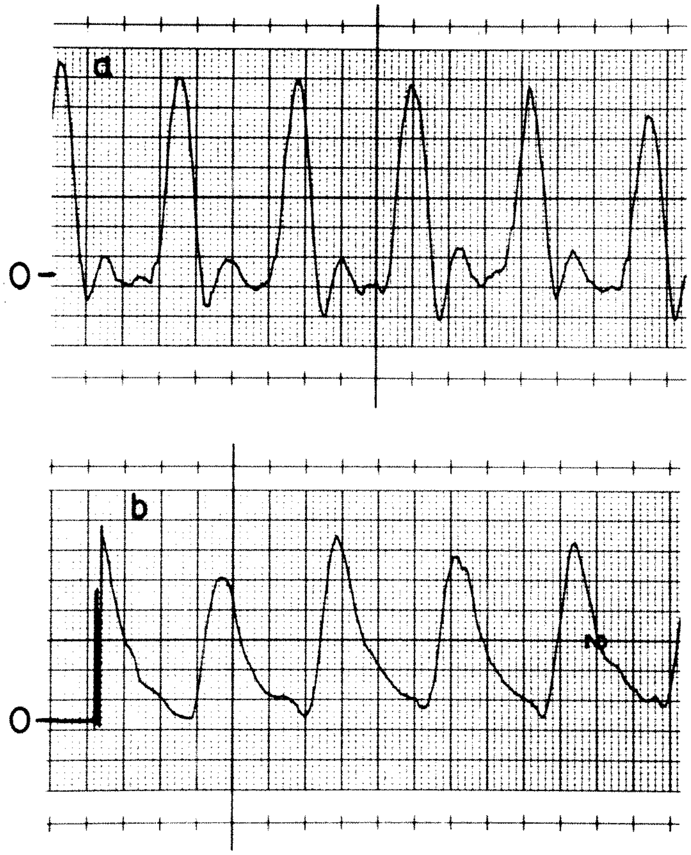


FIG. 1. A-Left, and B-Right brachial artery flow pattern. The lack of pulsatility noted in the right brachial artery is characteristic of proximal obstruction.

arm the magnitude of the vertebral steal increased by 83% (Fig. 2) and the right carotid flow decreased by 38% (Fig. 3). Minimal increases in antegrade flow in the left vertebral and carotid arteries were noted. An aortic arch arteriogram was then performed which demonstrated complete occlusion of the innominate at its origin, and retrograde right vertebral flow.

Case 2. A 43-year-old man had a history of faintness and visual blurring. The patient was well until 2 months prior to admission when he developed episodic faintness. These episodes lasted a few minutes and were associated with distorted vision.

On physical examination, the systolic pressure in the left arm was 126 mm. Hg and 94 mm. Hg in the right arm. The right radial pulse was decreased to palpation, and lagged in time behind the left. No pulse was palpable in the right carotid artery. A soft left carotid bruit was noted low in the neck. Neurologic findings were absent.

Flow tracings were obtained using the directional ultrasonic velocity detector. As in the previous case abnormal flow patterns were noted in the right brachial and carotid vessels and reversed flow was noted in the right vertebral artery. When hyperemia was induced in the right arm retrograde vertebral flow increased by 100% and right carotid flow decreased by 45%. Small increases in antegrade left carotid and vertebral flow were observed. An aortic-arch arteriogram (Fig. 4) revealed high grade stenosis of the innominate artery and stenosis of the left carotid artery at its origin. The left internal and external carotid arteries were also narrowed.

Case 3. A 71-year-old man complained of sudden dizziness. The pertinent history dated back to 1965 when he developed left hemiparesis. In 1966, a dissecting aneurysm of the aorta was successfully treated surgically but he was left with absent right carotid and radial pulses. He had no neurologic complaints until November 1970, when he experienced episodic confusion, disorientation, and blurred vision. An aortic arch study done at that time revealed total occlusion of innominate artery with retrograde right vertebral flow. No retrograde flow was noted in the right carotid artery. The patient underwent ligation of the right vertebral artery which partially relieved the symptoms. About one year following this procedure however, he developed drop attacks which have persisted until the present admission.

On physical examination, the patient was alert and oriented. Blood pressure in the right arm was 80/70 mm. Hg and 130/80 mm. Hg in the left arm. The pulses in the right arm and right carotid were not palpable. Neurologic examination revealed slight straightening of the nasolabial fold and some difficulty with left hand coordination. Flow studies with the directional ultrasonic velocity detector were carried out. Abnormal flow patterns, similar to those observed in the previous two patients, were noted in the right brachial artery. No right vertebral signals were obtainable. Carotid blood flow was reversed and, under the influence of right arm hyperemia, increased by 386% (Fig. 5). When the right carotid artery was momentarily compressed, flow in the right brachial decreased 15% (Figure 6).

Discussion

Wylie and Ehrenfeld[20] have found occlusion of the innominate artery in only 1.5% of patients with extracranial cerebrovascular disease. Approximately 10% of

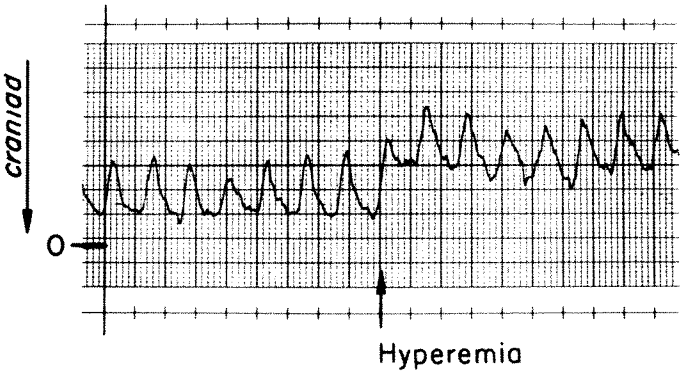


FIG. 2. Reversed flow in right vertebral artery. Flow increased by 83% when hyperemia was induced in the right arm.

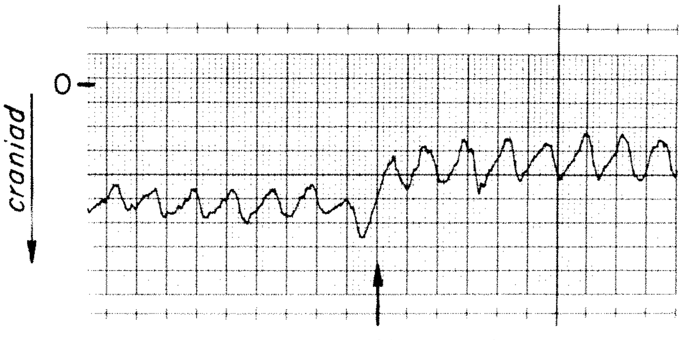


FIG. 3. Antegrade flow in right carotid artery. Flow decreased by 38% when hyperemia was induced in the right arm.

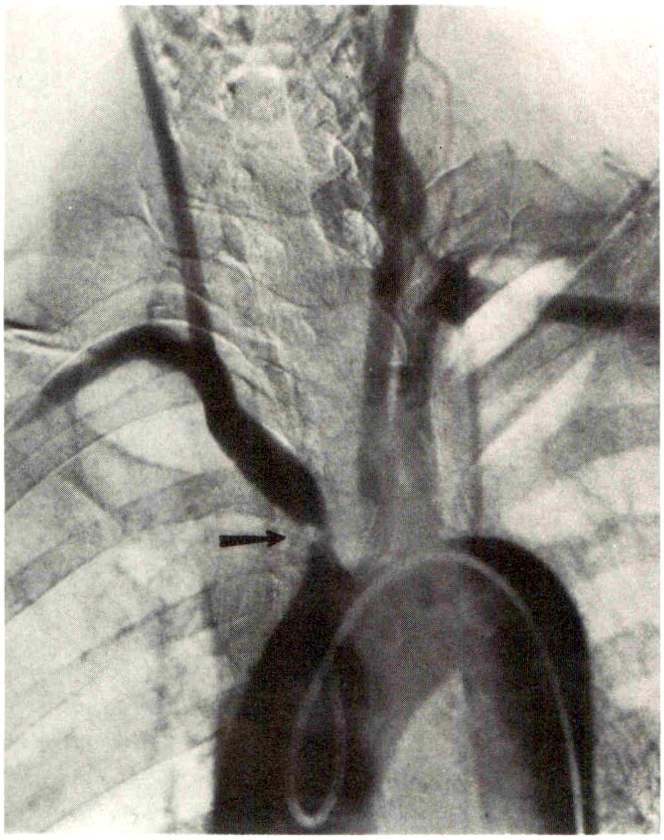


Fig. 4. Subtraction prints of aortic arch arteriogram. Arrow indicates area of stenosis in innominate artery.

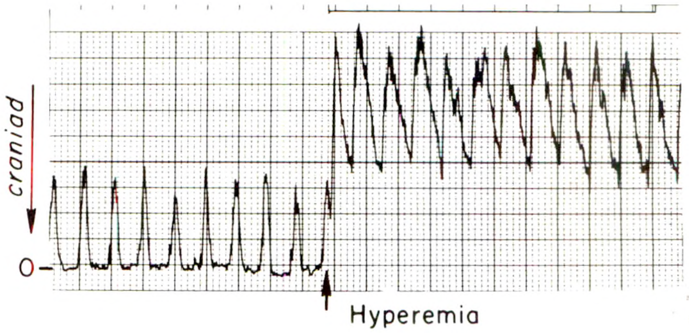


Fig. 5. Reversed flow in right carotid artery. Flow increased by 386% when hyperemia was induced in the right arm.

patients with symptomatic retrograde vertebral flow have innominate artery occlusion.[12] The present studies would indicate that the hemodynamic defect is much more severe, and the collateral circulation more complicated in these patients than when retrograde vertebral flow is produced by isolated subclavian occlusion.

The suggestion that symptoms of cerebral ischemia might be related to arm exercise in patients with retrograde vertebral blood flow secondary to subclavian or innominate stenosis was initially made by Reivich *et al.*[17] Although these authors provided some experimental evidence to show that total intracranial blood flow might be decreased as much as 40% when vertebral flow was reversed, more recent investigations have raised significant questions concerning the hemodynamic effects of subclavian occlusion. Hardesty[9] has estimated that only 11% of total cerebral flow reaches the brain by way of the vertebral arteries. When the subclavian artery is ligated, the flow in the vertebral artery is reversed, but of roughly the same magnitude as the antegrade flow prior to subclavian ligation. Handa and associates[7] have found that total cerebral blood flow in monkeys is very nearly constant regardless of whether or not the subclavian artery is ligated. Blood flow in the remaining vessels increases sufficiently to nearly compensate for the effect of vertebral flow reversal. These findings were confirmed in the dog by Eklof and Schwartz[4] who could demonstrate no change in cerebral blood flow or EEG activity in the presence of reversed vertebral flow. These authors were unable to demonstrate any decrease in cerebral blood flow until extensive ligation of the other extracranial vessels was added to the subclavian occlusion.

These experimental considerations probably explain the clinical observations that patients with isolated subclavian stenosis are rarely symptomatic[10,14,15,19] and that exercise is rarely responsible for the production of symptoms.[14,15,19] The present study would indicate, that patients with innominate artery occlusion have much more significant alterations in their extracranial hemodynamics.

The collateral pathways in patients 1 and 2 are summarized in Figure 7. Both patients demonstrated the "carotid recovery phenomenon" first suggested by Killen and Gobbel.[12] Blood entering the brain via the left vertebral and (probably to a lesser degree) left carotid artery is "stolen" by the right vertebral vessel. This blood is then used to perfuse not only the arm but is also "recovered" by the right carotid artery. We have clearly

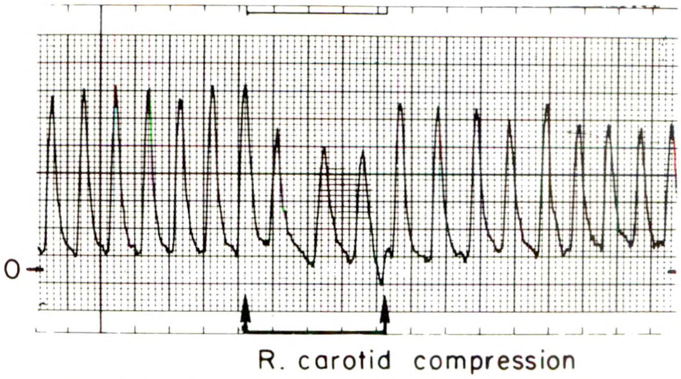


Fig. 6. Right brachial flow showing obstructed type tracing. Right carotid compression reduced brachial flow by 15%.

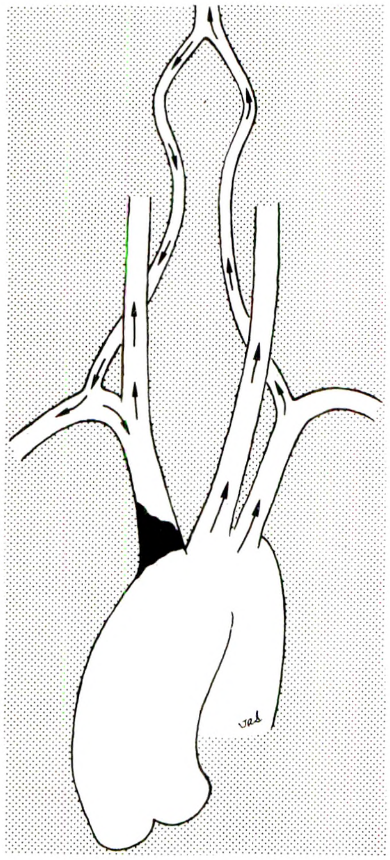


FIG. 7. Collateral pathway in patients 1 and 2. Blood "stolen" by right vertebral perfuses right carotid as well as right brachial arteries.

demonstrated that at times when the demands of the arm are increased, the magnitude of the vertebral "steal" is increased and the flow in the right carotid is reduced significantly. When the resistance of vessels in the circle of Willis is low or when the right vertebral is stenotic or occluded, flow may also be reversed in the right carotid artery. This situation has been reported previously but is not frequently encountered.[12,16] Patient 3 demonstrated retrograde right carotid flow, which contributed significantly to the blood supply of his arm. This was noted however, only after his vertebral artery had been ligated.

Thus in the presence of innominate artery occlusion, blood is supplied to the right side of the brain by means of collateral routes involving the circle of Willis. When blood is supplied to the brain by collateral pathways generalized or localized ischemic areas may develop, and symptoms may readily result. Handa and associates[8] have found that total cerebral blood flow in monkeys is reduced an average of 18% when the innominate artery is occluded.

The directional ultrasonic velocity detector has been a helpful diagnostic instrument in the evaluation of these patients. Most previous reports have depended upon radiographic technics to elucidate the pathways by which blood is supplied to the brain. Gonzales *et al.*[6] have suggested that radiographic of evaluation may be misleading. These authors have demonstrated radiographic evidence of retrograde vertebral flow in 8.3% of normal patients. The methods of evaluation we have used permit investigation of the flow patterns not only at rest but also under the influence of arm hyperemia. In this way, both a static and functional assessment of blood flow can be obtained quickly without harm or inconvenience to the patient.

Two main approaches to the therapy of this lesion have been advocated. Most authors have recommended the re-establishment of normal hemodynamic relationships by means of either endarterectomy or bypass procedures. Rob[18] has suggested vertebral artery ligation as an alternative in the poor-risk patient. Patient three demonstrates the inadequacy of vertebral artery ligation. In this case, retrograde carotid blood flow was generated after this operation was performed. Since most surgical approaches to this problem have necessitated the use of thoracotomy, correction of these lesions has been a major surgical problem. Two alternative methods of therapy may be effective in restoring normal hemodynamics without thoracotomy. The subclavian-subclavian bypass originally suggested by Ehrenfeld *et al.*,[5] and the subcutaneous axillary-axillary bypass[11,13] may be helpful in this regard.

Blakemore[1] has suggested that patients with innominate artery stenosis have a distinct clinical entity which he has termed the "innominate artery steal." While it is true that this term is less alliterative than the "subclavian steal syndrome," we feel that the therapeutic, clinical and hemodynamic differences which these patients display warrant their consideration as a separate group.

Summary

Three patients with innominate artery occlusive disease have been evaluated using the directional ultrasonic velocity detector. Two patients demonstrated reversed flow in the right vertebral artery and antegrade flow in the right carotid. In the third case, the vertebral artery had been ligated previously and retrograde flow in the right carotid artery was noted. The effect of right arm hyperemia on the flow in the extracranial cerebral vessels has been evaluated and the diagnostic, therapeutic, and prognostic implications of these findings are discussed.

References

1. Blakemore, W. S., Hardesty, W. H., Bevilacqua, J. E. and Tristan, T. A.: Reversal of Blood Flow in the Right Vertebral Artery Accompanying Occlusion of the Innonominate Artery. Ann. Surg., **161**:353, 1964.
2. Contorni L.: Il circold collaterale vertebro-vertebrale nella obliterazione dell arteria succlavia alla sue origine. Minerva Chir., **15**:268, 1960.

3. Editorial: A New Vascular Syndrome—"The Subclavian Steal." N. Engl. J. Med., **265**:912, 1961.
4. Eklof, B. and Schwartz, J. I.: Effects of Subclavian Steal and Compromised Cephalic Blood Flow on Cerebral Circulation. Surgery, **68**:431, 1969.
5. Ehrenfeld, W. K., Levin, S. M. and Wylie E. J.: Venous Crossover Bypass Grafts for Arterial Insufficiency. Ann. Surg., **167**:287, 1968.
6. Gonzalez, L., Weintraub, R. A., Wiot, J. F. and Lewis C.: Retrograde Vertebral Artery Blood Flow—a Normal Phenomenon. Radiology, **82**:211, 1964.
7. Handa, J., Ishikawa, S., Huber, P. and Meyer, J. S.: Experimental Production of the "Subclavian Steal." Electromagnetic Flow Measurements in the Monkey. Surgery, **58**: 703, 1965.
8. Handa, J., Yoshida, K. and Meyer, J. S.: Hemodynamic Effects of Subclavian and Innominate Artery Ligation. Surgery, **59**:1069, 1966.
9. Hardesty, W. H., Whitacre, W. B., Toole, J. F., Randall, P. and Royster, H. P.: Studies on Vertebral Blood Flow in Man. Surg. Gynecol. Obstet., **116**:662, 1963.
10. Irvine, W. T., Luck, R. J. and Jacobey, J. A.: Reversed Blood Flow in the Vertebral Arteries Causing Recurrent Brainstem Ischemia. Lancet, **1**:994, 1965.
11. Jacobson, J. H., II, Mozersky, D. J., Mitty, H. A., and Brothers, M. J.: Axillary-axillary Bypass for the "Subclavian Steal" Syndrome. Arch. Surg., **106**:24, 1973.
12. Killen, D. A. and Gobbel, W. G.: Subclavian Steal-carotid Recovery Phenomenon. J. Thorac. Cardiovasc. Surg., **50**: 421, 1965.
13. Mozersky, D. J., Sumner, D. S., Barnes, R. W. and Strandness, D. E., Jr.: Subclavian Revascularization by Means of a Subcutaneous Axillary-axillary Graft. Arch. Surg. **106**: 20–23, 1973.
14. North, R. R., Field, W. S., De Bakey, M. E. and Crawford, E. S.: Brachial-basilar Insufficiency Syndrome. Neurology, **12**:810, 1962.
15. Patel, A. and Toole, J. F.: Subclavian Steal Syndrome-reversal of Cephalic Blood Flow. Medicine, **44**:289, 1965.
16. Ramirez-Boettner, C. M., Sosa, O. D., Balanza, J. and Calcena, R. M.: Subclavian Steal Syndrome with Reversal of Blood Flow in the Right Carotid Artery. Ann. Intern. Med., **64**: 142, 1966.
17. Reivich, M., Holling, H. E., Roberts, B. and Toole, J. F.: Reversal of Blood Flow Through the Vertebral Artery and Its Effect on Cerebral Circulation. N. Engl. J. Med., **265**: 878, 1961.
18. Rob, C.: Incipient Strokes. Technique of Surgical Therapy. *In*: Milliken, C. H., Siekert R. G. and Whisnant, J. P., Eds. Cerebral Vascular Diseases. New York, Grune and Stratton, 1961:P.112.
19. Wheeler, H. B.: Surgical treatment of Subclavian-artery Occlusion. N. Engl. J. Med., **276**:711, 1967.
20. Wylie, E. J. and Ehrenfeld, W. K.: Extracranial Occlusive Cerebrovascular Disease. W. B. Saunders Co., Philadelphia, 1970.

Cardiac Aspects of Shock

Effects of an Ischemic Body on a Non-Ischemic Heart

A. MAZOR, M.D.,* S. ROGEL, M.D.

From the Cardiac Physiology Laboratory, Hadassah University Hospital, Jerusalem, Israel

IT HAS BEEN shown that in clinical or experimental hemorrhagic shock the heart is depressed.[8,15] The effect of this cardiac factor on the mortality rate is, however, disputed. Guyton and Crowell[3,7,6] believe that myocardial injury by the shock is of utmost importance, whereas Lillehi and co-workers[12] relate the cardiac changes to terminal alterations.

Two mechanisms have been suggested to induce myocardial impairment in hemorrhagic shock 1) local ischemia of the heart due to diminished coronary flow, and 2) humoral and neurogenic effects during a generalized tissue hypoperfusion. It is also possible that both these mechanisms affect the heart simultaneously.

The present work was undertaken to evaluate the effect of shock on the heart when it performs external work similar to the control condition, but the heart in itself has a normal amount of coronary perfusion with blood returning from the entire circulatory system in condition of profound hemorrhagic shock. This was achieved by designing an experimental model in which the animal is in shock apart from its heart.

Material and Methods

Sixteen mongrel dogs were anesthetized with intravenous sodium pentobarbital (30 mg./Kg.) and intubated for subsequent positive pressure ventilation (Bird respirator). The heart and great vessels were exposed through a longitudinal sternal split. A Walton-Brodie strain gauge arch was sutured to the right ventricular wall with the feet stretched to measure isometric myocardial tension. Right atrial and peripheral arterial pressures were obtained through catheters attached to Statham pressure transducers. Total cardiac output [CO] was measured by a Statham electromagnetic flowmeter placed around the main pulmonary artery. Thoracic aortic flow as well as the coronary arterial blood flow [CBF] (descending branch of the left coronary artery) were also obtained through electromagnetic flowmeter probes. All the above tension, pressure and flow measurements and a surface lead electrocardiogram were simultaneously recorded on a Hewlett-Packard eight channel thermal recorder. Stroke volume was obtained by dividing the cardiac output (read from the calibrated scale of the flowmeter) by the prevailing heart rate. Left ventricular work was calculated by multiplying cardiac output and mean aortic pressure just above the orifice of the coronary arteries. Dividing this work by heart rate gave the left ventricular stroke work. The internal work of the heart was calculated as heart rate times myocardial peak tension. The dog's urinary output was collected through a catheter placed in the urinary bladder. Arterial blood pH was measured by a Beckman pH meter. Arterial lactate concentration was determined according to the method of Loomis.[13] These measurements were taken before the production of the shock and every 30 minutes thereafter up to the end of the experiment.

A special circuit was designed to enable control of the perfusion pressure of the coronary arteries and of the venous return at all times as required. It consisted of a reservoir kept above the dog's heart and connected through a large bore cannula and tubing to the ascend-

---

Submitted for publication March 22, 1972.

* On leave of absence from the Department of General Surgery, Ichilov Municipality Hospital, Tel-Aviv, Israel.

Request reprints S. Rogel, M.D., Hadassah University Hospital, Jerusalem, Israel.

ing aorta and through another large bore tubing and cannula to the right atrium. Three screw clamps were placed around the ascending aorta above the insertion of the cannula and on both tubes which determined the amount of blood pumped by the ventricle, through the ascending aorta, into the reservoir and the volume returning from the reservoir into the right atrium. The blood returning to the right ventricle was thus composed of the venous return through the great veins and the blood coming from the reservoir. The experimental set-up is diagrammed in Figure 1.

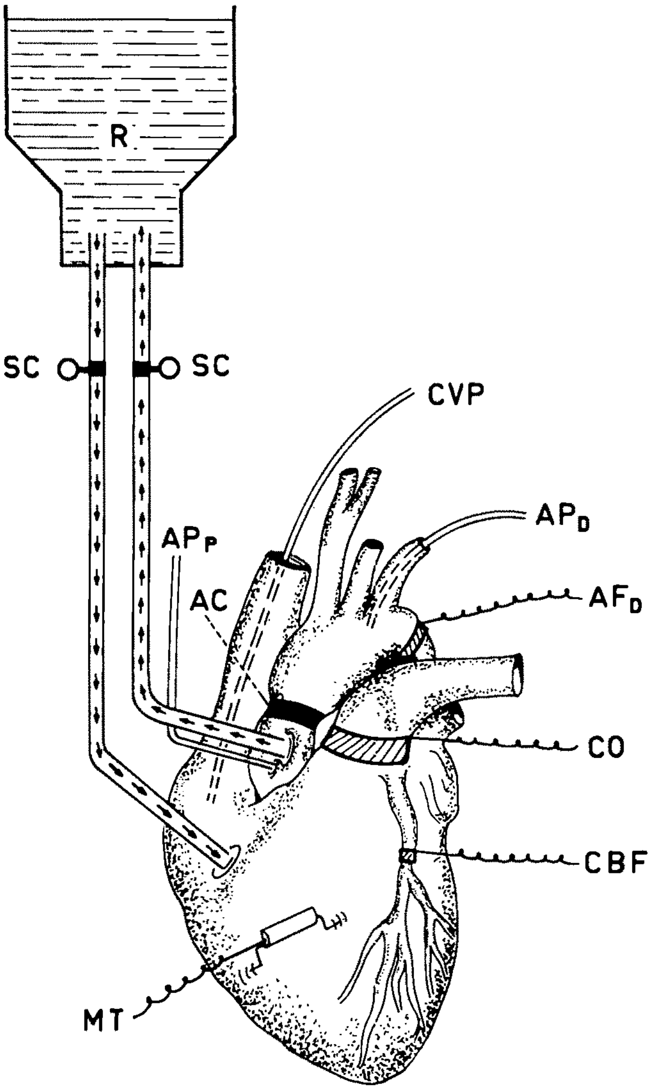


Fig. 1. A diagramatic illustration of the experimental set-up. The dog is bled to shock level and the ascending aorta is constricted (AC). From the proximal aorta blood is pumped by the heart into the reservoir (R) at a rate which can be controlled by a screw clamp (SC) and permits maintenance of proximal aortic blood pressure (AP_P) and coronary blood flow (CBF) at control level. From the reservoir blood can be reinfused (regulated by SC) into the right atrium at a rate which maintains, together with the venous return from the shocked body, a cardiac output (CO) and a central venous pressure (CVP) as during the control state. Blood flow (AF_D) and pressure (AP_D) distal to the aortic constriction are also measured. A strain gage arch sewn to the right ventricular wall measured isometric myocardial tension (MT).

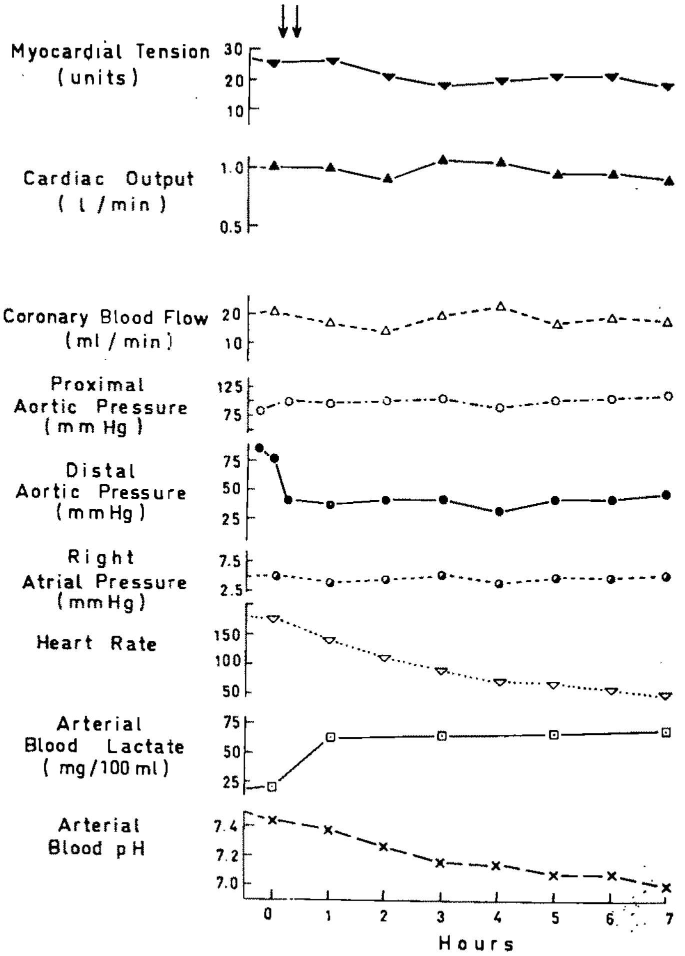


Fig. 2. Hemorrhagic shock (induced between the two arrows) in a dog with maintained coronary circulation. Note the diminished distal aortic blood pressure, decreasing pH and increasing blood lactate as signs of shock, as opposed to cardiac output, coronary flow, proximal aortic and right atrial pressures which are kept at control levels.

All the above described measurements were performed at the steady control condition. Thereafter, hemorrhagic shock was induced by bleeding the dog from its aorta into the reservoir until the mean systolic pressure could be kept steadily below 50 mm. Hg. The coronary arteries were protected against such low pressure by partial constriction of the ascending aorta distal to the tube leading to the reservoir. By this method coronary pressure and flow could be maintained around control levels while the whole body was hypotensive. To maintain cardiac output close to the control level and thereby impose on the ventricles about the same amount of work during shock as during the control stage, the venous return was regulated by changing the return of blood from the reservoir into the right atrium. All the hemodynamic parameters which have been measured be-

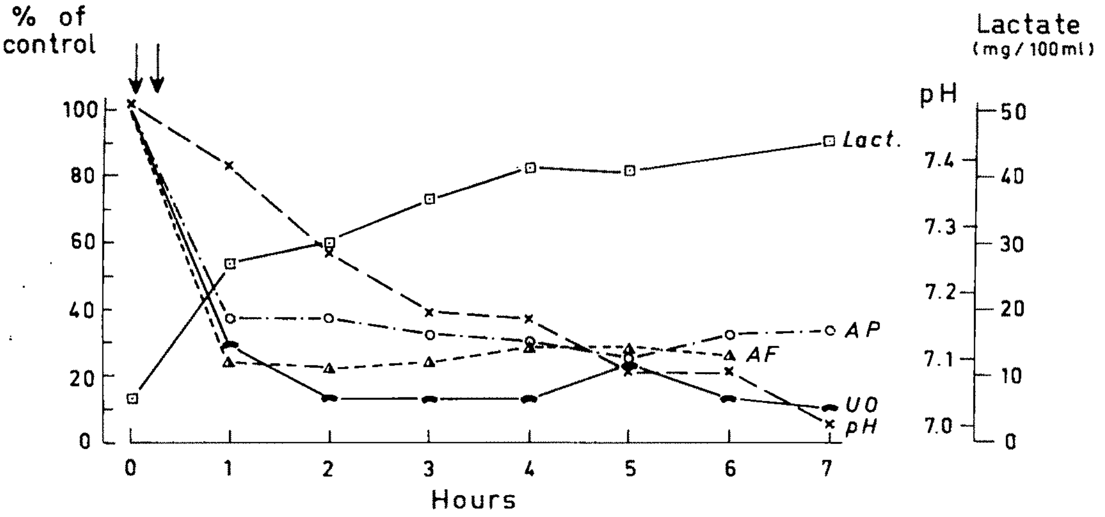


FIG. 3. The average values of various parameters indicating very marked tissue hypoperfusion (short of the heart) in 11 dogs. A.P. = blood pressure in the descending aorta. A.F. = descending aortic blood flow. U.O. = urinary output. pH = arterial blood pH. Lact. = arterial blood lactate concentration. Shock induced between the two arrows.

fore the induction of shock have continuously been measured after initiation of shock and throughout the experiment until the dog died.

In five dogs the same experimental procedure, including the state of hemorrhagic shock, was performed without altering the spontaneously developed coronary perfusion pressure, coronary flow and systemic venous return.

Results

A representative tracing of a single experiment is illustrated in Figure 2 exhibiting the time sequence, direction and magnitude of changes of the various parameters in a dog with ischemic body but non-ischemic heart. However, the results of all the experiments will be shown as average values for the group of dogs with hemorrhagic shock not including the heart as well as average values for the control group.

The proof that all the animals were in a profound state of shock can be seen in Figure 3. It shows that the arterial mean pressure declined from its control level of 128 mm. Hg (100%) to 47 mm. Hg (37%) after the first hour of shock and remained about a third of its control level until the end of the experiment.

There was a concomitant and marked drop in the descending aortic flow to 24% of the control value during the first hour of shock and stayed so thereafter. The arterial pH gradually decreased from 7.48 to 7.17 after 3 hours and to 7.00 at the time of death.

As expected, the urinary output decreased from an average of 31 ml./hr. to 9 ml./hr. after the first hour and to 3–4 ml/hr. throughout the shock period. The average arterial blood lactate concentration was initially 6.7 mg./100 ml. increasing to 26.9 mg./100 ml. in the first hour of shock and gradually elevated to 45 mg./100 ml.

Generally, in dogs exhibiting the above described classic signs of shock, the arterial pressure, cardiac output and coronary flow are reduced markedly and continue to decline until the death of the animal. For the purpose of checking our model and methods of measurements, these parameters have been obtained in five control dogs. Figure 4 shows that the results were as expected.

The special technic used in the present study enabled us to achieve our purpose of maintaining a fairly steady proximal aortic pressure, cardiac output, and coronary blood flow at about control levels (Fig. 5) during the presence of profound shock.

Figure 6 summarizes the measured or calculated data from the group of dogs in which the heart was kept well perfused with the blood coming from the shocked body. On the average, the myocardial tension changed slightly even after 5 hours (90% of control) and decreased to about 75% thereafter. The internal work of the heart, however, decreased more since there was a marked and gradual diminution of the heart rate to 60% of the control level after the first hour of shock and to below 40% at the end of the experiments. Slowing of heart rate, in the presence of cardiac output maintained to control levels, indicates, of course, a progressive rise of stroke volume. Indeed, the stroke volume more than doubled as time progressed. The stroke work of the heart increased parallel to the rise of stroke volume and almost doubled itself as the rate declined. The external left ventricular work progressively decreased in the first 3 hours and remained around 60% of the control value thereafter.

Figure 7 demonstrates the corresponding average values for a group of five dogs in which the hearts were exposed to all the hemodynamic conditions of shock. Myocardial tension approached 60% of its control value in the 3rd hour of shock. Moreover, all the parameters

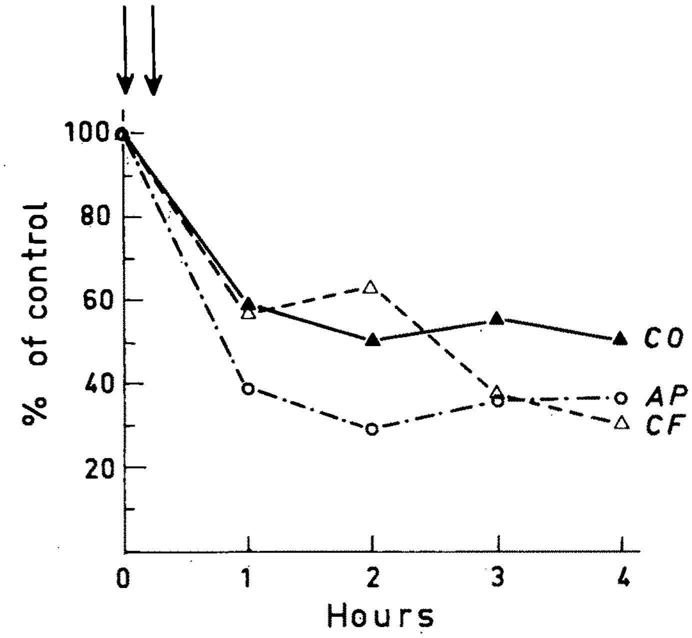


FIG. 4. The average aortic pressure (A.P.), cardiac output (C.O.), and coronary flow (C.F.) in five control animals during hemorrhagic shock (induced between the two arrows).

showed a marked decrease in the first hour and the minimal values were much lower during the experiment than in the study group of animals. The stroke work diminished markedly despite the slowing rate and the transiently elevated stroke volume due to excessive drop of aortic pressure.

Discussion

Generally, in hemorrhagic shock progressive circulatory failure ensues. However, there is considerable dispute as to the mechanism of this phenomenon. Wiggers[13] had observed that the fall in the systemic pressure follows an initial reduction of cardiac output and thus he assumed that the primary cause of circulatory failure is the diminished venous return. However, in many cases even restoration of normal venous return cannot prevent irreversible changes indicating that factors other than venous return shall initiate the fatal outcome. Reduced blood volume or continuous loss of fluid from the vascular compartment has been suggested by some authors to be a responsible mechanism.[9] Sarnoff and co-workers[14] described an increased left ventricular end-diastolic pressure accompanying the hypotensive state which, however, could be reversed artificially by improved coronary flow. Their suggestion was, therefore, that myocardial depression due to inadequate coronary perfusion may cause the cardiac failure. Contrary to these observations, Gomez and Hamilton[4] have shown in animals in shock, short of the head and upper limbs, that perfusion of the coronary arteries at normal pressure does not prevent the development of heart failure at sudden volume load into the left atrium. They have ascribed this to a release of cardiotoxic substances from the hypotensive part of the body. The importance of coronary flow was emphasized again by Jones and associates[10] who found a protective effect of pharmacologically induced coronary vasodilation against the development of irreversible hemorrhagic shock. Crowell and Guyton[3] have also proved the development of cardiac failure in the course of hemorrhagic shock demonstrating increased filling pressures even at normal cardiac output levels. Lillehei and associates,[12] conversely, expressed views that myocardial depression is a secondary phenomenon induced only by peripheral vascular changes which cause diminished return to the heart. They have also pointed out the importance of metabolic changes in the blood such as acidosis and stressed the necessity for immediate and proper correction of the blood pH to restore adequate myocardial function.

The negative inotropic effect of metabolic acidosis on the left ventricular function was also described by Wildenthal and co-workers.[17] They have attributed this to direct depression of left ventricular contractility and depressed ventricular responsiveness to cathecholamines. Left ventricular contractile force was not found, however, to be reduced in the first hour of severe oligemic hypotension unless irreversible state of shock has taken place.[2] More recent works of Lefer and co-workers indicate the presence of a humoral factor, myocardial depressant factor (m.d.f.) in the blood of animals in severe shock.[11,15] This substance was shown to be a polypeptide released by proteolytic activity present in the blood during shock.

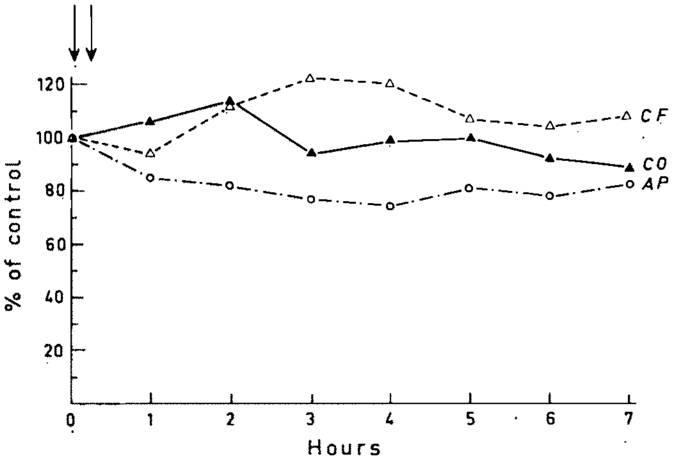


FIG. 5. The average values of proximal aortic pressure (A.P.), cardiac output (C.O.), and coronary blood flow (C.F.) in 11 dogs with ischemic body but well perfused heart (shock induced between the two arrows).

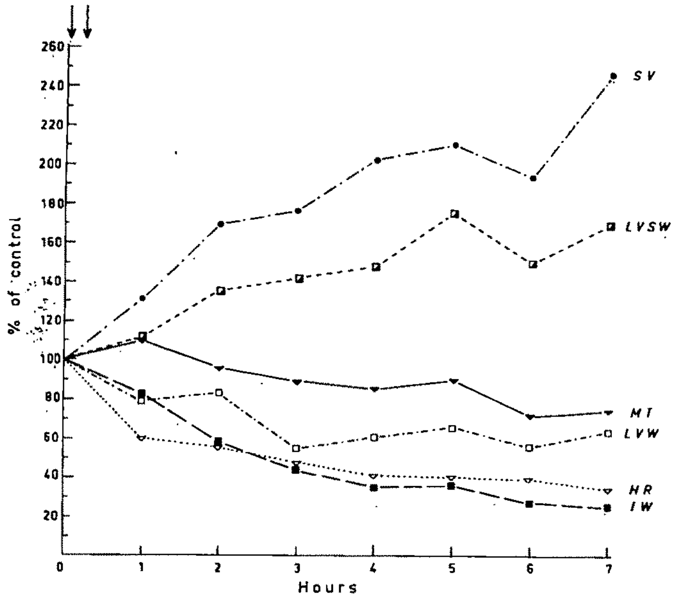


FIG. 6. The average values of the various measured or calculated parameters in 11 dogs during maintained coronary circulation with blood returning from the ischemic body. Note the slow decline of myocardial tension (MT) and marked rise of stroke work (LVSW) due to progressive decrease of heart rate (HR). SV = stroke volume, LVW = left ventricular work, IW = internal work. Shock induced between the two arrows.

Due to this considerable dispute on the mechanism by which the state of shock influences myocardial performance, an experimental model was designed to elucidate this problem. The experimental set-up prevented the development of some conditions claimed to depress cardiovascular function such as a drop of venous return, cardiac output, coronary perfusion pressure and coronary blood flow. By doing so, two main possibilities have remained open: 1) some reflex mechanism acting through the autonomic nervous system and 2) humoral factors brought to the heart by the blood draining the ischemic body. This may include normal metabolites, like hydrogen or lactate ions, but in increased amounts or abnormal metabolites as myocardial depressant factor or other undefined substances.[1,17]

Our experimental model was designed to separate between the role of local ischemia in the heart and peripheral ischemia on the heart. If there is any humoral factor in the blood its cardiac effect should be even more evident, since it is perfusing the heart in larger quantities due to the maintained coronary blood flow as opposed to reduced coronary flow in the usual state of shock. Also, if there is a myocardial depressing effect it should become more easily detectable since the cardiac work is maintained at a higher level by the near normal cardiac output and control proximal aortic pressure, than during the regular state of shock.

The results presented in this study show that if the dogs were bled and their hearts were also subjected to the overall effects of shock, the cardiac output, coronary flow, arterial pressure, left ventricular internal and external work and myocardial tension have all decreased to 50% or below the control values within 2 hours and led to early death. Only the stroke volume did not decrease (or even become transiently elevated) since the pulse rate has steadily decreased during the experiment. Such a progressive slowing of the heart was a constant feature of all experiments performed.

In the group of dogs in which the state of shock manifested itself in a similar manner as in the control group, the heart was prevented from local ischemia, but was required to control activity, being perfused with blood coming from the shocked tissues. The first striking phenomenon was a few hours longer survival and a much less prominent decrease in myocardial tension than in the control group (not more than 15% during the first 5 hours of shock and only about 22% after 7 hours). There was a progressive drop of heart rate throughout the experiment which together with the maintained cardiac output and aortic pressure caused a steady increase in stroke volume and work until there was a sudden terminal decrease. These values are different from those obtained in the control experiments and led to the following conclusions: The myocardium is able to contract fairly well even if it is perfused with blood coming from a shocked body, provided the coronary flow is kept normal. Under these conditions the heart may also increase its stroke work if adequate venous return is available. Although the survival of the animals is considerably prolonged, the perfusion

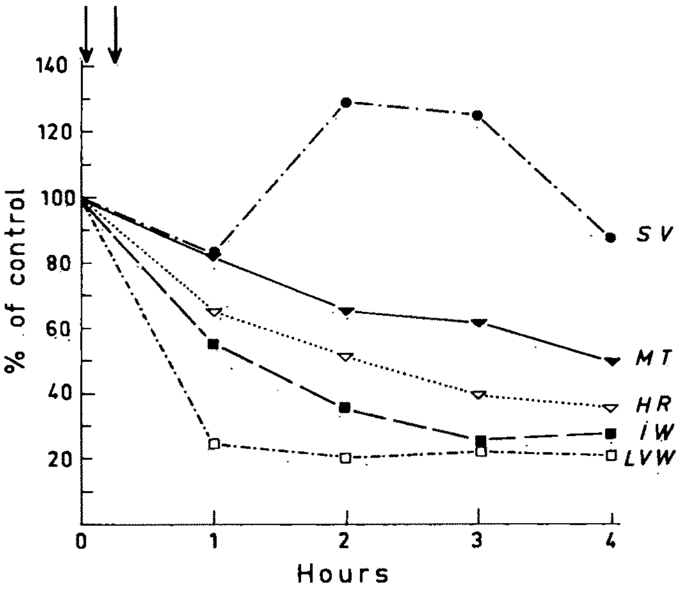


FIG. 7. The same parameters as in Figure 5 measured or calculated in the control group. The deterioration of myocardial function is more marked and starts earlier than in the study group (symbols as in Fig. 5).

of the myocardium by the blood with low pH and a high lactate concentration, and perhaps containing myocardial depressant factors, leads to a slow deterioration of cardiac function, though much less evident than in the control group.

Summary

In open-chest dogs hemorrhagic shock was induced using an experimental model in which coronary perfusion pressure, coronary blood flow and cardiac output were maintained close to control levels. Thus the whole animal was kept in deep shock except for the heart which was perfused with the blood returning from the shocked body.

It was found that under these conditions myocardial tension dropped only slightly during the course of time, while the stroke work became elevated due to slowing of the heart. The internal work decreased markedly and so did the external work even though to a much less extent. The survival was longer than in the control animals. The results seem to indicate that the reduced coronary perfusion in the control dogs leads to early myocardial depression and death. However, the progressive but slow decline in the group with adequate coronary pressure and flow may indicate that late consequences of shock on the heart are probably induced by the composition of blood arising from the periphery in shock.

References

1. Caress, D. L., Kissack, A. S., Slovin, A. J. and Stuckey, J. H.: The Effect of Respiratory and Metabolic Acidosis on Myocardial Contractility. J. Thorac. Cardiovasc. Surg., **56**:571, 1968.
2. Cooley, J. C. and McIntosh, C. L.: Myocardial Contractile Force in Experimental Hemorrhagic shock. Arch. Surg., **87**:330, 1963.
3. Crowell, J. W. and Guyton, A. C.: Cardiac Deterioration in Shock: The Irreversible Stage. *In:* Shock, Ed., Hershey, S. G., Boston, Little Brown and Co. p. 13, 1964.
4. Gomez, O. A. and Hamilton, W. F.: Functional Cardiac Deterioration during Development of Hemorrhagic Circulatory Deficiency. Circ. Res., **14**:327, 1964.
5. Gregg, D. E. and Fisher, L. C.: Blood Supply to the Heart. *In:* Handbook of Physiology. Circulation, Ed. Hamilton, W. F. and Dow, P. Washington, American Physiology Society, Sect. 2, vol. II, p. 1517, 1963.
6. Guyton, A. C. and Crowell, J. W.: Dynamics of the Heart in Shock. Fed. Proc., **20**:51, 1961 (Suppl. 9).
7. Guyton, A. C. and Crowell, J. W.: Cardiac Deterioration in Shock: Its Progressive Nature. *In:* Shock, Ed., Hershey, S. G. Boston, Little Brown and Co. 1964.
8. Hardaway, R. M.: Clinical Management of Shock. Springfield, Ill., Charles C Thomas, 1968.
9. Hollenberg, N. K., Waters, J. R., Toews, M. R., Davies, R. O. and Nickerson, M.: Nature of Cardiovascular Decompensation during Hemorrhagic Hypotension. Am. J. Physiol., **219**:1476, 1970.
10. Jones, C. E., Bethea, H. L., Smith, E. E. and Crowell, J. W.: The Effect of a Coronary Vasodilator on the Development of Irreversible Hemorrhagic Shock. Surgery, **68**:356, 1970.
11. Lefer, A. M.: Role of a Myocardial Depressant Factor in the Pathogenesis of Circulatory Shock. Fed. Proc., **29**: 1836, 1970.
12. Lillehei, R. C., Longerheam, J. K., Bloch, J. H. and Manax, W. G.: The Nature of Irreversible Shock: Experimental and Clinical Observations. Ann. Surg., **160**:682, 1964.
13. Loomis, M. E.: An Enzymatic Fluorometric Method for the Determination of Lactic Acid in Serum. J. Lab. Clin. Med., **57**:966, 1961.
14. Sarnoff, S. J., Case, R. B., Waithe, P. E. and Isaacs, J. P.: Insufficient Coronary Flow and Myocardial Failure as a Complicating Factor in Late Hemorrhagic Shock. Am. J. Physiol., **176**:439, 1954.
15. Wangensteen, S. L., Geissinger, W. T., Lovett, W. L., Glenn, T. M. and Lefer, A. M.: Relationship between Splanchnic Blood Flow and a Myocardial Depressant Factor in Endotoxin Shock. Surgery, **69**:410, 1971.
16. Wiggers, C. J.: Myocardial Depression in Shock. A Survey of Cardiodynamic Studies. Am. Heart J., **33**:633, 1947.
17. Wildenthal, K., Mierzwiak, D. S., Myers, R. W. and Mitchell, J. H.: Effects of Acute Lactic Acidosis on Left Ventricular Performance. Am. J. Physiol., **214**:1352, 1968.

LIBRARY

Surgical Management of the Dialysis Patient

MAKOTO HATA, M.D., AUGUST R. REMMERS, JR., M.D.,
JAMES D. LINDLEY, M.D., HARRY E. SARLES, M.D.,
JAY C. FISH, M.D.

*From the Departments of Surgery and Medicine,
The University of Texas Medical Branch,
Galveston, Texas 77550*

MAJOR OPERATIONS upon patients on maintenance dialysis involve risks not associated with patients who have adequate renal function. These include the metabolic and clinical consequences of uremia such as poor wound healing, increased susceptibility to infection, bleeding tendency, fluid overload and hyperkalemia. Diminution of these risks should be accomplished by adequate preoperative dialysis and early resumption of postoperative dialysis. Extracorporeal hemodialysis requires heparinization, and even the carefully managed regional heparinization technic may result in anticoagulation of the patient. Subsequent bleeding from the operative site may then result in the need for earlier repeated dialyses to manage the hyperkalemia and azotemia resulting from absorption of the extravasated blood. A disastrous circular pattern of dialysis, anticoagulation, bleeding, hyperkalemia, and more dialysis, anticoagulation, and bleeding is established.

Early in our experience with cadaveric renal transplantation, a number of complications resulted from bleeding and delayed wound healing. These complications were often attributable to the lack of recent dialysis before operation resulting in a moderate degree of uremia and the need for dialysis early in the postoperative period.

Patients undergoing major operative procedures who may require postoperative dialysis include those on maintenance dialysis, patients receiving renal transplants, and patients with acute renal failure. Because of additional variables such as immunosuppressive drugs in the renal transplant patients and prior injuries, infections, intoxications or other variables in the acute renal failure patients, only the chronic maintenance dialysis patients were examined in detail in this report. These patients more clearly demonstrate the single effect of operation upon the functionally anephric patient.

Patient Protocol

Based on our previous experiences, a new protocol was designed. The essential features were 1) extracorporeal hemodialysis within 24 hours of the operation, 2) insertion of a Silastic peritoneal dialysis catheter at the time of operation, 3) postoperative dialysis via the peritoneal route during the first several days in those patients in whom anticoagulation would be a major risk, 4) resumption of the first hemodialysis by the regional anticoagulation technic and, if uncomplicated, subsequent dialyses with system anticoagulation, and 5) preoperative blood transfusion for hypovolemia, and/or a hematocrit of less than 25%, administered during dialysis.

During the period from January, 1968, to January, 1971, 60 patients were trained for unattended home dialysis. All patients were dialyzed with a Kiil artificial kidney[1] using a Drake-Willock delivery system.[3] An external arteriovenous shunt was routinely used. Patients were dialyzed three times a week at night while asleep for a total of 24 to 30 hours of dialysis per week. The diet consisted of 80 Gm. of high biological quality protein with 1,500 to 2,500 calories per day with some variation for age, sex, weight, and activity. Chemical control was monitored by weekly pre- and post-dialysis analysis of the blood chemistries.

Submitted for publication May 30, 1972.

Supported in part by USPHS contract No. HSM-110-71-195 and DHEW 1 PO1 AI 09278-01.

Reprint requests: Dr. Jay C. Fish, Department of Surgery, The University of Texas Medical Branch, Galveston, Texas 77550.

Results

Seventeen of the 60 patients have undergone 26 major operative procedures. All but three of the operations were elective [Table 1]. The indication for operation was bleeding associated with dialysis in nine patients. These included three nephrectomies, four hysterectomies, one lumbar artery aneurysmectomy, and one suprapatellar synovectomy. The indications for all but two of the remaining operations were for the complications of chronic renal failure, *i.e.*, nephrectomy for hypertension, four; Thomas shunts[6] for dialysis, five; parathyroidectomy for tertiary hyperparathyroidism, four; Pearman prosthesis[4] for priapism, one; and iliac arteriorraphy for arterial occlusion resulting from retrograde catheter aortography, one. One patient was re-explored for retroperitoneal bleeding following nephrectomy and one patient had an elective splenectomy for hemolytic anemia.

TABLE 1. *Major Operations in Seventeen Dialysis Patients*

Nephrectomy	7
Thomas Shunt[6]	5
Hysterectomy	4
Parathyroidectomy	4
Splenectomy	1
Iliac Arteriorraphy	1
Suprapatellar Synovectomy	1
Lumbar Aneurysmectomy	1
Pearman Prosthesis[4]	1
Evacuation Retroperitoneal Hematoma	1
	26

Preoperative Data

Before 24 of the operative procedures, the patients were dialyzed during the 24-hour period prior to operation, using systemic heparinization in 12 and regional heparinization in seven. Peritoneal dialysis was used in five in preparation for operation of patients without an A-V shunt or because of a very recent bleeding episode. In the other two patients, dialysis was last performed 3 days prior to an emergency operation. The mean preoperative laboratory values were blood urea nitrogen, 39 mg./100 ml.; serum creatinine, 6.1 mg./100 ml.; and hematocrit, 25%.

Blood was administered preoperatively during the last dialysis in 11 patients for replacement of blood loss or to raise the hematocrit to 25%. No patient had evidence of volume overload, uremia, hyperkalemia, or an electrolyte imbalance at the time of operation. Five patients had significant fall in blood pressure during induction of anesthesia. All five responded to blood and saline administration.

Operative Management

Bilateral nephrectomies were performed through anterior transverse incisions via an extraperitoneal dissection except for polycystic kidneys which were removed transperitoneally [Table 1]. Dacron patch applique shunts (Thomas shunt)[6] were applied to the femoral vessels on three occasions and required two revisions for a total of five operations.

In all but eight patients a Silastic peritoneal dialysis catheter[*][5] was inserted prior to the completion of the operation. The eight without a catheter included seven in whom postoperative hemodialysis and possible anticoagulation were not contraindicated.

Postoperative Management

Serum potassium levels were monitored every 4 hours during the first postoperative day and every 12 hours thereafter. The indications for peritoneal dialysis were a potassium level greater than 5.5 meq/L, a rapid increase in blood urea levels, or routinely on the second or third postoperative day. In three of the 18 patients with a peritoneal catheter, no peritoneal dialysis was performed [Table 2]. In two of these the catheter was contaminated at the time of insertion and had to be removed within 48 hours. In the third case, no dialysis was indicated until the patient was re-started on routine hemodialysis with regional anticoagulation on the third day. Seven of the eight patients without a peritoneal catheter had uneventful postoperative courses. One patient did well until 18 days after the operation when he had two episodes of retroperitoneal bleeding while on dialysis at home. He was re-admitted and successfully managed without re-operation by peritoneal dialysis for 7 days.

The mean duration of postoperative peritoneal dialysis in the remaining 15 patients was 7 days. Some variation of this occurred according to the magnitude of operation and potential risk of a postoperative bleed

TABLE 2. *Postoperative Peritoneal Dialysis*

No. Operations	Peritoneal Catheters	Receiving Peritoneal Dialysis	Day Extracorporeal Hemodialysis Begun
26	Yes-18	Yes-15	before day 7-7
			after day 7-8
		No-3	3-3
	No-8		3-1

---

[*] Tenckhoff Peritoneal Dialysis Catheter, Seattle Artificial Kidney Supply Co. Seattle, Washington.

TABLE 3. *Postoperative Complications*

Bleeding		2
Required Transfusion	1	
No Transfusion	1	
Infection		3
Minor	2	
Major	1	
Allergic Drug Reaction		1
		6

with anticoagulation. Hemodialysis was begun earlier after the neck and extremity procedures and later after the intra-abdominal and retroperitoneal procedures.

Six postoperative complications occurred [Table 3]. The two minor infections were due to placement of contaminated peritoneal catheters inserted at the time of vaginal hysterectomy. The major infection was a pelvic abscess that drained through the vagina.

Postoperative blood transfusions were administered to eight patients. In one it was given for postoperative bleeding and the other seven received blood for hematocrits less than 20%.

During the first 2 days postoperatively, the most common indication for dialysis was a rising serum potassium. Levels above 5.5 meq/L often occurred within the first 24 hours. Figure 1 is an example of the use of peritoneal dialysis for the management of recurrent hyperkalemia.

Discussion

One of the surprising findings in this study was that 28% of the patients trained in a chronic home dialysis program over the past 4 years required a major operative procedure. In addition, the indication for operation was related to end-stage renal disease, its consequences, or the treatment of that disease (dialysis) in all but one patient. Hampers *et al.*[2] reported 44 operations in 33 patients. Only two of the operative procedures were performed for conditions unrelated to chronic renal failure or dialysis.

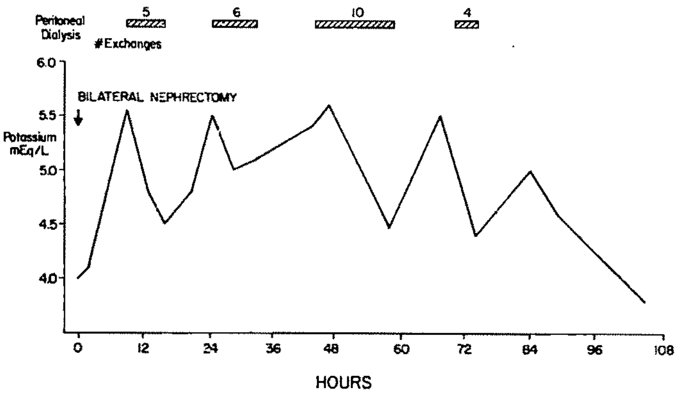


FIG. 1. This patient had an uneventful elective bilateral nephrectomy. He had no clinical evidence of bleeding and did not require blood transfusions. Nevertheless, he had four separate episodes of rising serum potassium during the first 3 days that were managed by peritoneal dialysis.

The principal aims of the preoperative dialysis were to ensure maximum metabolic control and avoid fluid overload and hyperkalemia. Excessive removal of fluid undoubtedly resulted in the hypotension seen in five patients during the induction of anesthesia. All responded to the administration of 300 to 500 ml. of blood or saline. It is obvious that correction of a volume deficit is infinitely simpler and safer than managing a volume overload in these patients.

No patient died and none were disabled as a result of major operation in this series.

Reducing postoperative bleeding by avoiding hemodialysis during the first few days was accomplished by peritoneal dialysis. The risk of postoperative bleeding from hemodialysis appears to far outweigh the risk of peritoneal infection from a catheter. We have used postoperative peritoneal dialysis routinely for the past 3 years in renal transplant, chronic dialysis, and in acute renal failure patients as early as 4 hours after abdominal surgery. Its use has not resulted in abdominal wound complications nor interference with the healing of intra-abdominal gastrointestinal or vascular anastomoses. No septic complications have followed its use that have not responded to removal of the catheter and antibiotic therapy.

Management of the rising serum potassium is simplified by the limited use of peritoneal dialysis to control that single parameter when there is no other indication for dialysis. The advantages of having a peritoneal catheter in place postoperatively can be summarized as 1) immediate access for dialysis, 2) no special personnel or equipment are required for institution of dialysis, 3) ease with which limited amounts of dialysis may be repeated, and 4) anticoagulation is not required.

Regular dialysis by one of the methods is continued postoperatively to allow for the early resumption of a diet. From this experience, there appears to be no discernible delay in wound healing or susceptibility to infection in the well nourished, well dialyzed patient with chronic renal failure.

Summary

Two important considerations separate patients with renal failure from the ordinary surgical population. They are the consequences of uremia upon general biologic function and the effects of the treatment of uremia, specifically anticoagulation for dialysis.

In a group of 60 home dialysis patients, 17 required

26 operative procedures. In all but one of these the operation resulted from the consequences of the renal failure or its treatment, *i.e.* bleeding following anticoagulation during dialysis.

There were six postoperative complications and no deaths. Management of the renal failure included dialysis during the 24 hours prior to operation, and on a routine basis postoperatively. Anticoagulation was avoided in the early postoperative period, by the routine use of peritoneal dialysis in those patients in which postoperative bleeding was a reasonable possibility. The most common indication for early institution of dialysis following operation was a rising serum potassium. This problem was most easily managed by the limited use of repeated peritoneal dialyses.

References

1. Cole, J. J., Pollard, T. L. and Murray, J. S.: Studies on the Modified Polypropylene Kiil Dialyzer. Trans. Am. Soc. Artif. Int. Organs, **9**:67, 1963.
2. Hampers, C. L., Bailey, A. L., Hager, E. B., Vandam, L. D. and Merrill, J. P.: Major Surgery in Patients on Maintenance Hemodialysis. Am. J. Surg., **115**:747, 1968.
3. Ivanovich, P., Marr, T. A., Gohlberg, L. A., Steury, R. E. and Drake, R. F.: A Compact Hydraulic Proportioning System for Hemodialysis. Trans. Am. Soc. Artif. Int. Organs, **12**: 357, 1966.
4. Pearman, R. O.: Treatment of Organic Impotence by Implantation of a Penile Prosthesis. J. Urol., **97**:716, 1967.
5. Tenckhoff, H. and Schechter, H.: A Bacteriologically Safe Peritoneal Access Device. Trans. Am. Soc. Artif. Int. Organs, **14**:181, 1968.
6. Thomas, G. L.: Large Vessel Applique Arteriovenous Shunt. A New Concept. Am. J. Surg., **120**:244, 1970.

Renal Parenchymal Tolerance to Artery Occlusion:

A Time and Damage Study in Rats Developing Collateral Circulation

P. K. DONAHOE, M.D.,* JOHN D. OSMOND, III, M.D.†
DAVID R. STEWART, M.D.,* W. HARDY HENDREN, III, M.D.*

From the Division of Pediatric Surgery & The Pediatric Surgical Research Laboratory, Massachusetts General Hospital and the Department of Surgery, Harvard Medical School, Boston, Massachusetts

ACUTE RENAL ARTERY OCCLUSION occurs in man from trauma and embolization. In order to evaluate the role of surgical intervention in these cases it is important to define the contribution of collateral blood vessels to renal blood flow. This study will describe observations of collateral blood flow, both immediate and long-term in the rat following acute renal artery occlusion, as demonstrated by microangiography. It will, in addition, describe the accompanying histologic changes in the kidney.

Methods and Materials

Sprague-Dawley 6-week-old female rats were fed a standard laboratory diet, supplemented by antibiotics for 3 days following operation. Young rats were chosen to take advantage of the stimulatory effect of growth hormone upon collateralization.[9]

Group I. In 45 rats the left renal artery was divided, followed by Micropaque perfusion studies at intervals varying from 1 hour to 97 days, to demonstrate patterns of collateral blood flow to the kidney.

Group II. In 10 rats the left renal artery was divided, and the right kidney was simultaneously removed, to determine if pre-existing collaterals were sufficient to sustain life.

Group III. In six animals the left renal artery was temporarily ligated for intervals of 20 minutes to 4 hours, after which the ligature was released, and flow to the kidney reestablished for 10 minutes, to demonstrate the earliest or most sensitive site of ischemic injury. Micropaque studies were then performed.

Microangiographic Technic

Micropaque is a finely divided barium sulfate suspension of 4 to 10 microns particle size.[10] Selective regional perfusion was performed by injecting micropaque into the aorta via a polyethylene catheter just below the renal arteries with the aorta ligated above the celiac axis and below the level of insertion of the catheter. 200 units of USP Heparin were injected prior to perfusion to prevent thrombus formation. A 15% Micropaque and saline suspension was perfused at a pressure of 100 mm. Hg for 20 minutes; pressure was kept constant with a mercury release bath. The inferior vena cava was partially divided to provide an egress for the perfusate. Animals were then prepared for histologic examination by immersion in 10% formalin for 24 hours; perfusion was continued at 3 feet of gravity pressure. Radiographs of the specimens were then made using a Faxitron 805 x-ray unit with a Beryllium window and a 0.5 mm. focal spot. The factors for radiography were 30 KV, 3 mA, and 4 minutes. One mm paraffin imbedded sections of the left kidney were made and further radiographs taken at factors of 30 KV, 3 mA and 1 minute. Stereoscopic pair x-rays were analyzed in a Stereorealist viewer providing 8 to 10 times magnification. Further radiographs of selected specimens were taken using high resolution plates pro-

---

Submitted for publication April 5, 1972.

* Division of Pediatric Surgery and the Pediatric Surgical Research Laboratory, Massachusetts General Hospital and the Department of Surgery, Harvard Medical School, Boston, Mass.

† Departments of Radiology of Massachusetts General Hospital and Harvard Medical School.

Reprint requests to: W. H. Hendren, M.D., Massachusetts General Hospital, Boston, Mass. 02114.

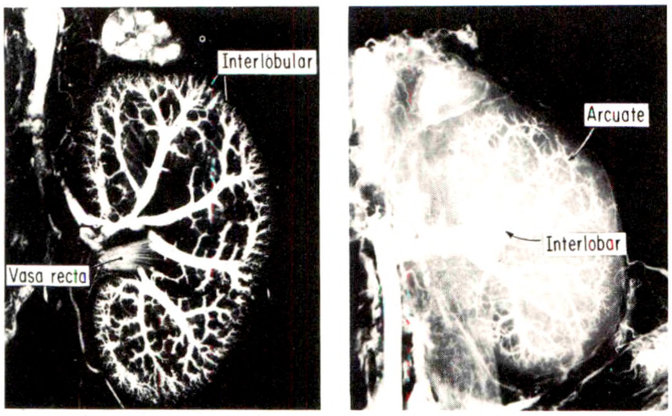


FIG. 1a (left). Micropaque perfusion of normal rat kidney (1 mm section) showing interlobar, interlobular and arcuate vessels. Glomeruli are well filled but can not be appreciated at this magnification. Vasa recta are well filled. 1b (right). Micropaque perfusion of whole rat kidney 2 hours after division of the renal artery. Micropaque fills the arcuate vessels and a few interlobular vessels.

viding magnification capabilities of 300 ×. Representative histologic sections were stained with hematoxalin and eosin.

Results

Group I. Division of Main Renal Artery

a) 1-2 hours. Micropaque perfusion filled the major interlobar, arcuate, interlobular arteries, and a few afferent arterioles, showing that pre-existing collaterals are present and patent immediately when the main renal artery is occluded. However, histologic examination showed early degeneration of tubules, and nonfilling of glomeruli and vasa recta. Figure 1a shows perfusion of a normal rat kidney; Figure 1b shows a rat kidney perfused 2 hours after ligation of its renal artery.

b) 3–4 hours. Micropaque filling stopped at the arcuate vessels. Histology showed further tubular necrosis and early glomerular damage (Fig. 2).

c) 7–24 hours. Micropaque perfusion showed nonfilling of the intrarenal vessels. The preexisting collaterals noted at 1 to 4 hours became dilated and tortuous. Histology showed progressive damage of cortex and medulla, except for the cortex nearest to the hilum of the kidney. Thus, although collaterals are present, they can not sustain the kidney; there is stasis in the vessels, followed by thrombosis, and then renal necrosis. Figure 3a & b show the microvascular anatomy and histology of a kidney from this group.

d) 5–12 days. Micropaque perfusion showed filling of interlobar vessels but not their branches; collaterals increased progressively in size, number and tortuosity. Histology showed progressive renal destruction except for the parahilar cortex (Fig. 4a & b).

e) 16–97 days. The kidney became progressively calcified, decreasing to one third of its original size. Micropaque perfusion showed continued filling of interlobar arteries, but nothing beyond, *i.e.*, no filling of arcuate, interlobular or glomerular arteries. Collat-

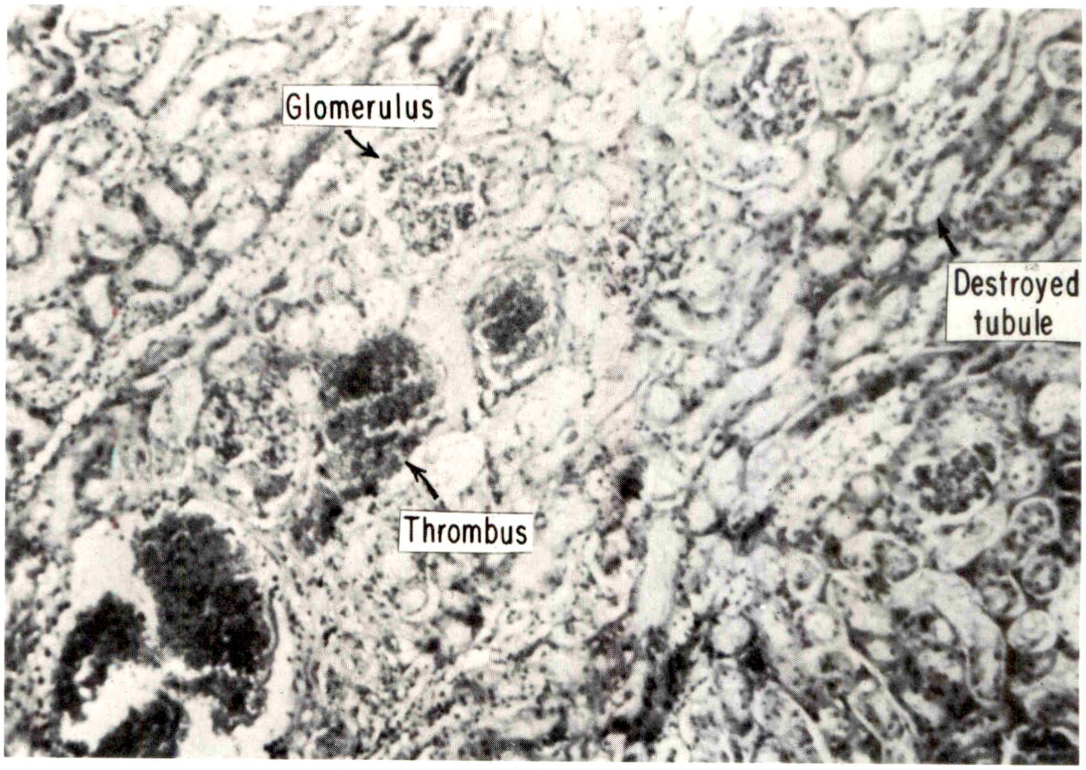


FIG. 2. 4 hours after division of the renal artery the cortex shows stasis, tubular destruction & non filling of the glomeruli with micropaque (100 ×)

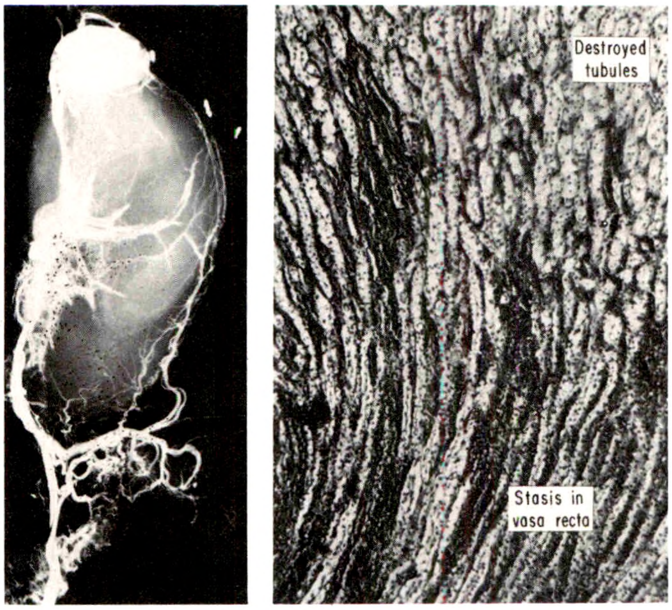


FIG. 3a (left). Micropaque perfusion of the rat kidney 24 hours after division. There is essentially no filling beyond the interlobar arteries. The collaterals are dilated and tortuous. 3b (right). Histologic sections show stasis in the vasa recta and tubular cellular destruction.

erals further increased in number, size, and tortuosity, but were ineffective to preserve the kidney (Fig. 5a & b).

Group II. Division of the Left Renal Artery and Right Nephrectomy

All of these rats died within 48 hours, proving that collaterals can not support a kidney after acute ligation of its main renal artery.

Group III. Temporary Occlusion

a) When the artery was occluded for less than 90 minutes, followed by 10 minutes of arterial reflow, micropaque perfusion showed filling of the glomeruli and vasa recta. Histology, however, showed tubular cellular damage as early as 40 minutes (Fig. 6).

b) When the artery was occluded for more than 90 minutes, followed by 10 minutes of reflow, micropaque did not fill vessels beyond the interlobular arteries. Histology showed stasis in the vasa recta and more tubular cellular damage. The glomeruli filled poorly except in the parahilar cortex (Fig. 7a & b).

Discussion

Collaterals to the kidney, come from six major sources[1,4,5,7,8,11] (Fig. 8): 1) *hilar,* from the aorta across the stump of the divided renal artery; 2) *adrenal,* to the superior capsule and distal renal artery; 3) *ovarian,* to the inferior capsule and the distal renal stump; 4) *ureteric,* to the inferior capsule and to the distal renal artery stump; 5) *lumbar,* to the posterior capsule and parahilar area and; 6) *inferior phrenic,* to the posterior and lateral capsule. In these experiments, the ureteric and ovarian collaterals showed the most striking enlargement with some vessels becoming nearly as large as the original renal artery.

The micropaque studies showed three phases of collateral revascularization: first, there is immediate filling via pre-existing vessels; second, there occurs dilatation and elongation of pre-existing vessels; finally, there is formation of new vessels. Perfusion studies at 1 to 4 hours after renal artery division fill the kidney but the collaterals are essentially no larger than seen on perfusion studies of a normal kideny. At 16–24 hours the pre-existing collaterals dilate, elongate, and become more tortuous when compared with the normal collateral anatomy. Neovascularization, as seen as a network of small, tortuous vessels at the hilum and around the capsule of the kidney, began between 1 and

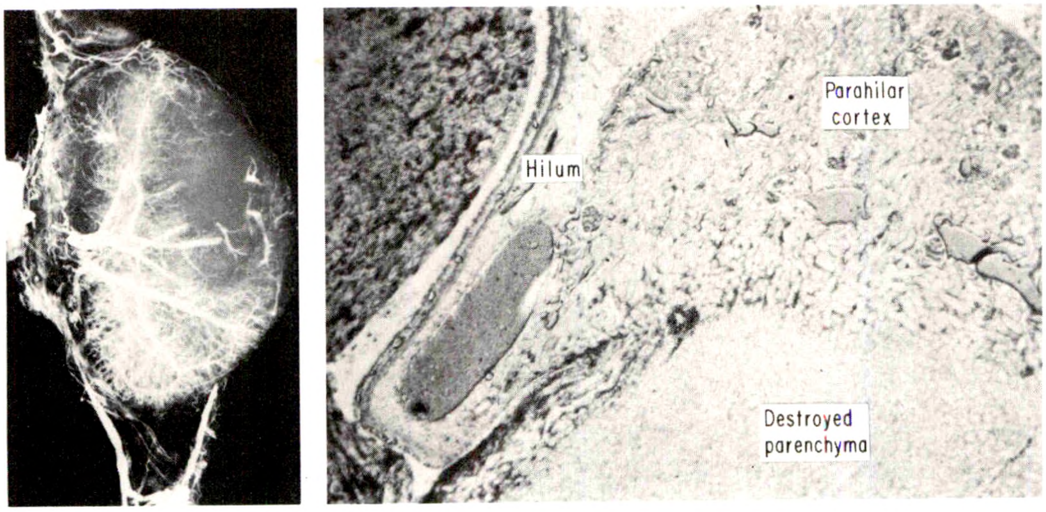


FIG. 4a (left). Micropaque perfusion at 5 days shows neovascularization of the collaterals and "pruning" of the interlobar vessels. 4b (right). Histologic sections demonstrate relative sparing of the parahilar cortex.

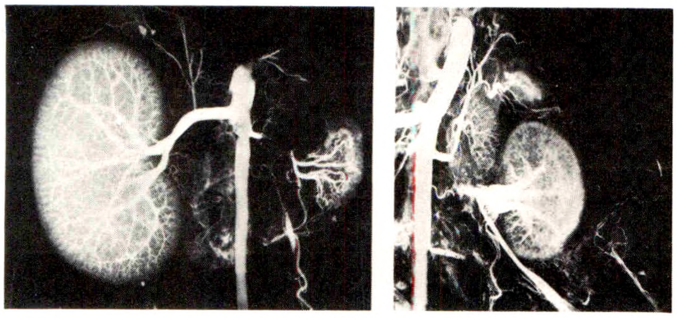


FIG. 5a (left). The left kidney at 97 days after division of the renal artery is markedly atrophic & calcified. The interlobar arteries fill well. 5b (right). Large collaterals develop around the ureter and from the ovary.

5 days and progressively increased to the end of the experiment, 97 days. Weibel[12] demonstrated by electron microscopy that neovascularization occurs in the rat lungs at 5 days after division of the main pulmonary artery. The delay in the development of these new vessels suggests that there may be a humoral mechanism involved similar to that which has been demonstrated by Folkman *et al.*,[16] to be responsible for the development of tumor vessels.

Immediate injury, as demonstrated by reflow studies, appears to be reflex, with shutdown of the efferent arterioles and vasa recta. This was pointed out by Diethelm and Wilson,[3] using carbon particle injections, and confirmed by the present micropaque studies. Heparin failed to reduce the damage, indicating that thrombosis was probably not important in this post glomerular obstruction of early renal ischemia.[3] Constriction of the vasa recta and efferent arterioles produces back pressure and stasis,[2] but flow from the collaterals is never sufficient to reopen the efferent arterioles; therefore, thrombosis occurs. The thrombus eventually un-

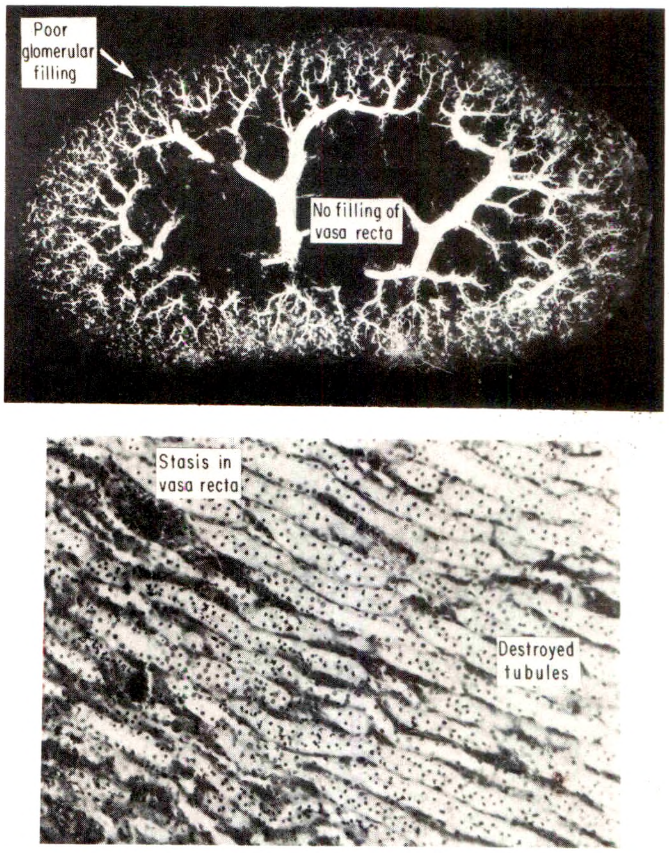


FIG. 7a (top). After 4 hours of temporary occlusion micropaque perfusion (1 mm section) shows very poor glomerular filling and non-filling of the vasa recta. 7b (bottom). The medullary area shows destroyed tubules and stasis in the vasa recta.

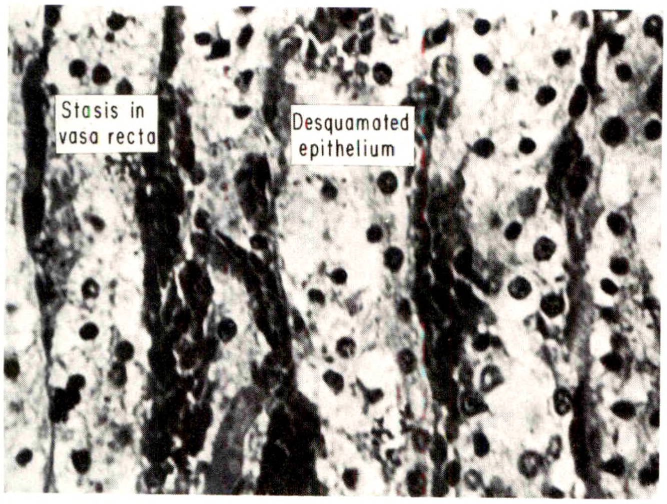


FIG. 6. After 40 minutes of temporary artery occlusion the medullary area shows widespread stasis in the vasa recta and desquamation of tubular epithelium (400 ×)

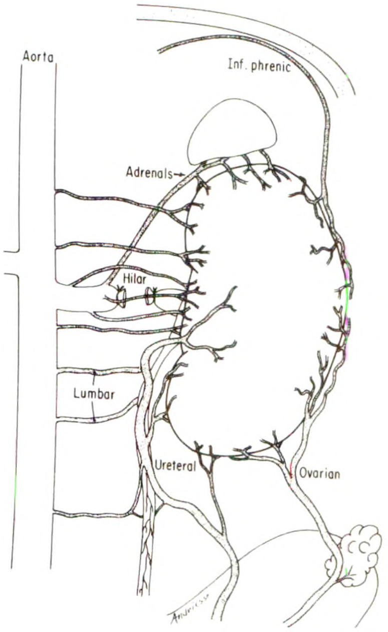


FIG. 8. Diagram of major collaterals to the rat kidney, after 30 days. Many of these major collaterals are often seen to go directly to the distal renal artery stump.

dergoes lysis leading to collateral refilling of the interlobar vessels, as noted in the later phases of the study.

Preservation of the parahilar cortex was observed from the first hour to the 97th day. As the rest of the kidney progressively atrophied, this area appeared viable, probably related to the concentration of collaterals around the hilum. There were no associated collecting tubules, however, and so, this small area of cortical preservation would likely not represent preservation of renal function.

Summary

Collaterals, consisting of pre-existing vessels and new vessels, contribute significantly to the blood supply of the ischemic rat kidney. They appear to spare preferentially the parahilar area of the kidney, but can not protect the kidney from necrosis when the renal artery is acutely divided. These studies suggest that salvage of a kidney after acute, complete renal artery occlusion or interruption must depend on reestablishment of its main arterial flow in a very short time, possibly within 90 minutes.

References

1. Abrams, H. L. and Cornell, S. H.: Patterns of Collateral Flow in Renal Ischemia. Radiology, **84**:1001, 1965.
2. Brodman, R., Hackett, R. and Pfoff, W.: Microangiography of the Renal Vasculature Following Ischemia. Surg. Forum, **20**:46, 1969.
3. Diethelm, A. G. and Wilson, S. J.: Obstruction to the Renal Microcirculation after Temporary Ischemia. J. Surg. Res., **11**:265, 1971.
4. Eliska, O.: Blood Flow Through the Collateral Circulation of the Kidney. Angiologica, **3**:333, 1966.
5. Eliska, O.: The Collateral Blood Flow of the Canine and Human Kidney. Cor Vasa **8**:68, 1966.
6. Folkman, J., Merler, E., Abernathy, C. and Williams, G.: Isolation of a Tumor Factor Responsible for Angiogenesis. J. Exper. Med., **133**:275, 1971.
7. Ljungvist, A.: Ischemic Renal Atrophy and Hypertension. Acta Chir. Scan. **132**:323, 1966.
8. Moffat, D. B. and Fourman, J.: The Vascular Pattern of the Rat Kidney. J. Anat. (London), **97**:543, 1963.
9. Meffert, W. and Liebow, A. A.: Hormonal Control of Collateral Circulation. Circ Res., **18**:228, 1966.
10. Rubin, R.: Microangiography: Facts and Artifacts. Radiol. Clin. N. Am., **2**:499, 1964.
11. Takahashi, M., Abrams, H. L., Palmer, J. M. and Obreg, T.: Collateral Arterial Development and Renal Function in Experimental Renal Hypertension. Invest. Radiol., **3**:108, 1968.
12. Weibel, E. R.: Early Stages in the Development of the Collateral Circulation to the Lung in the Rat. Circ. Res., **8**:353, 1960.

Worth using once

Made of 4-ply quilted cotton gauze with X-ray detectable element sewn into each sponge.

Pre-sterilized—always ready when you need them.

Double wrapped—for aseptic removal.

Disposable—to reduce the incidence of cross contamination.

Available in 4 sizes, with or without ring.

Write us for a sample and prices

SPARTA INSTRUMENT CORPORATION
205 FAIRFIELD AVENUE / FAIRFIELD, N.J. 07006 / (201) 575-1344

In 16 years of use in the United States, FLUOTHANE (halothane) has been administered over 100 million times in a wide variety of surgical procedures. 100 million ...extensive usage and evaluation that attests to FLUOTHANE as the most widely used inhalant anesthetic.

Since it was first introduced, over 4,000 papers worldwide have been published, ranging from review articles to in-depth studies. 4,000 papers... a bibliographic record of note on the most widely used inhalant anesthetic.

In a continuing program of informational services on anesthesiology, Ayerst provides printed and audiovisual aids reflecting the opinions and experiences of recognized authorities in the field. These include the highly regarded series on *Anesthesia Rounds* and *Clinical Aspects of Anesthesiology*, as well as several films of educational value—all available through your Ayerst Representative.

FLUOTHANE® (HALOTHANE) ...OVER 100 MILLION ADMINISTRATIONS

- nonflammable, nonexplosive
- permits use of high concentrations of oxygen
- allows free use of cautery for more adequate control of bleeding
- minimal odor facilitates smooth, rapid induction, reduces patient distress
- early obtundation of pharyngeal and laryngeal reflexes facilitates intubation
- lessens airway problems
- permits rapid adjustment of depth of anesthesia
- emergence is rapid and tranquil with quick recovery of protective reflexes
- minimal nausea and vomiting, shorter recovery room stay

Ayerst®

See last page of advertisement for prescribing information.

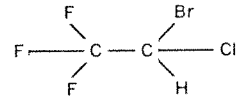
FLUOTHANE®
brand of halothane
the most widely used inhalant anesthetic

from **Ayerst**®

for precision, experience, quality, and service

(Complete text of package circular.)

Description. FLUOTHANE, brand of halothane, is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C., and the boiling point (range) is 49° C.-51° C. at 760 mm. Hg. The vapor pressure is 243 mm. Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C., and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. FLUOTHANE is soluble in rubber, some plastics, and similar materials; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizing bottles not specifically designed for its use. It is recommended that vaporizers be emptied at the end of each operating day. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE should be avoided when a previous exposure was followed by fever and jaundice, or when there was an unexplained postoperative fever.

FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy: Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. Cirrhosis or other abnormalities involving liver dysfunction, including a history of viral hepatitis, may be a basis for selecting an anesthetic other than a halogenated agent.

The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

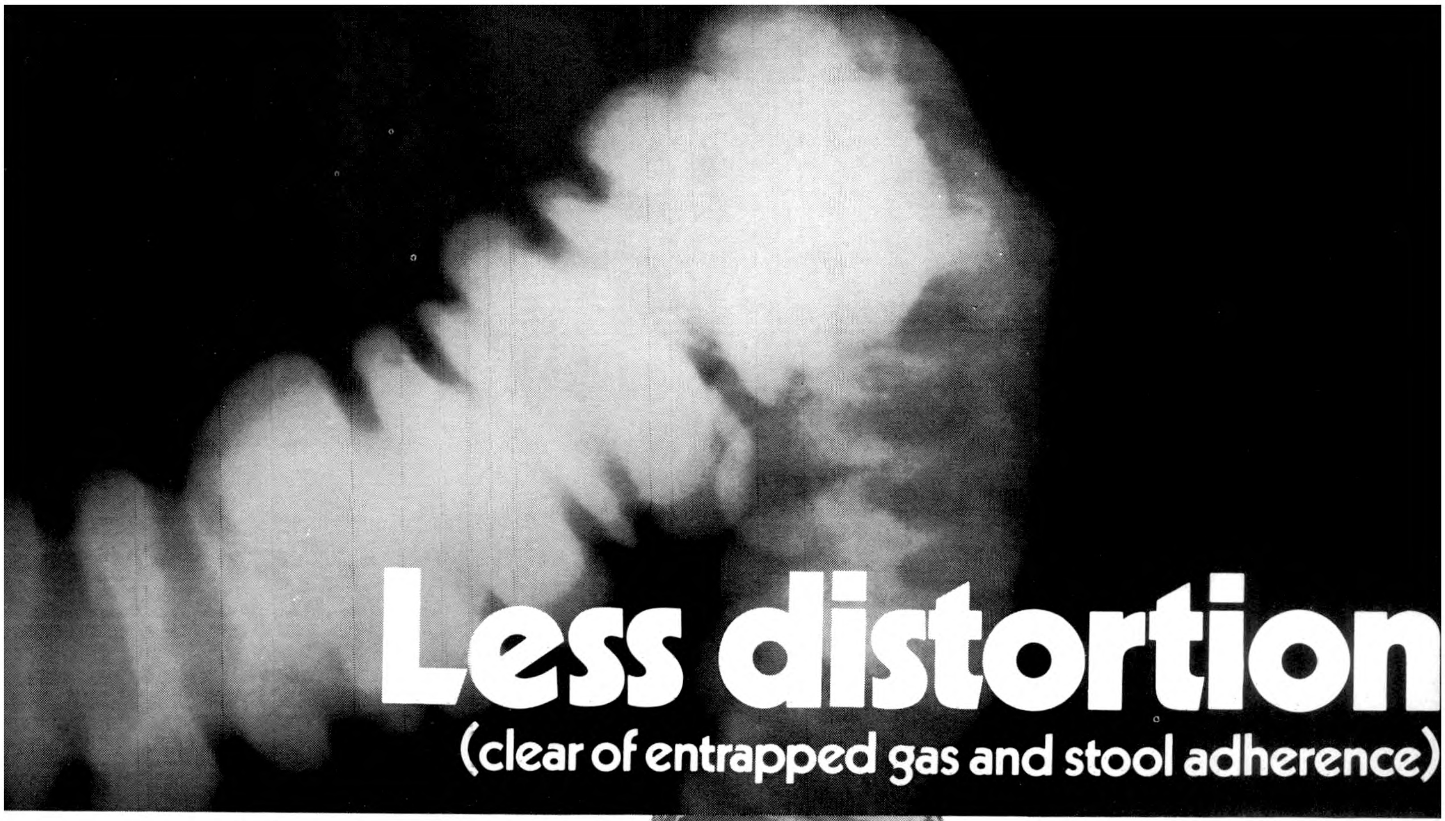
Adverse Reactions. The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

How Supplied. No. 3125—Unit packages of 125 cc. and 250 cc. of halothane stabilized with 0.01% thymol (w/w).

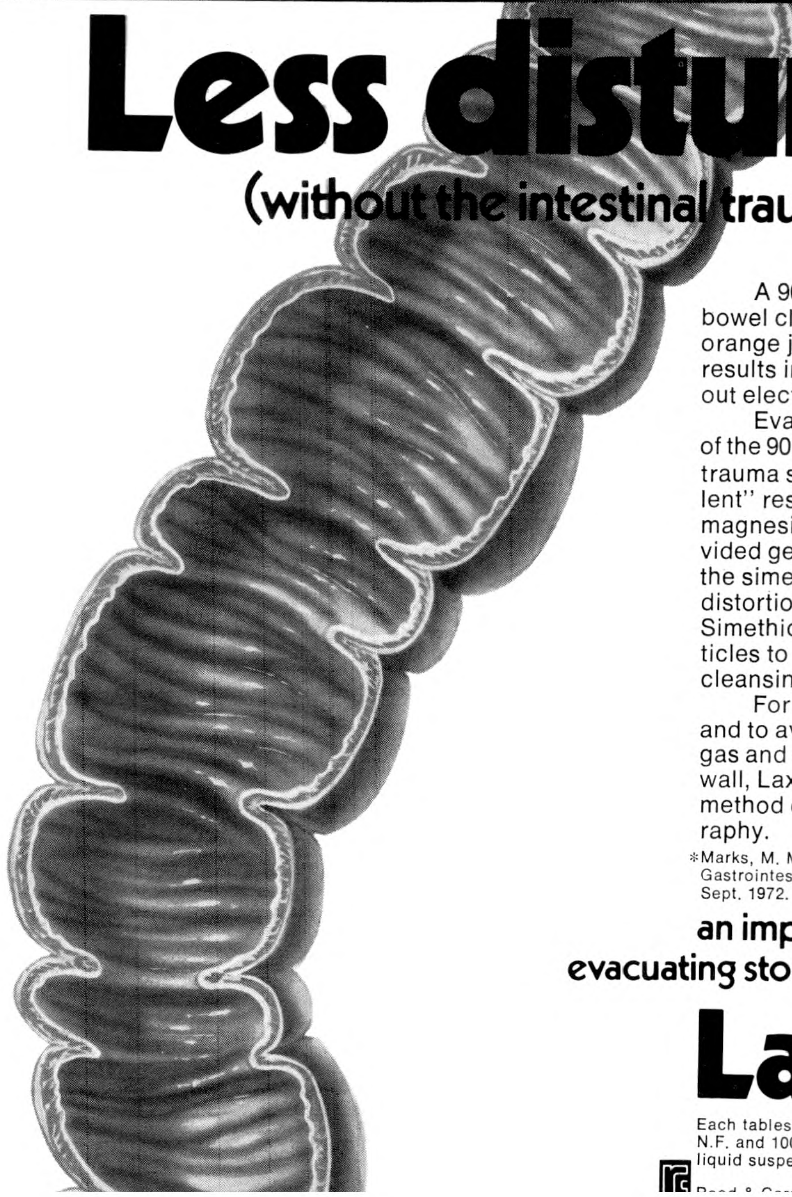
Ayerst® **AYERST LABORATORIES**
New York, N.Y. 10017

FLUOTHANE® (halothane) is available in the United States by arrangement with Imperial Chemical Industries Ltd. **7317**



Less distortion

(clear of entrapped gas and stool adherence)



Less disturbance

(without the intestinal trauma of harsh cathartics)

A 900-patient study* has demonstrated that bowel cleansing with a combination of Laxsil® and orange juice, unlike purging with harsh cathartics, results in "... a non-irritating watery stool ... without electrolyte, protein or excessive fluid loss."

Evaluations of rectal smears taken from each of the 900 patients to determine evidence of mucosal trauma showed that 99% had a "good" to "excellent" response. The study showed that while the magnesium hydroxide component of Laxsil provided gentle evacuation of solids, the inclusion of the simethicone in the formula overcame the visual distortion normally caused by entrapped gas. Simethicone also prevented adherence of stool particles to the bowel wall, eliminating the need for cleansing enemas.

For non-injurious evacuation of the G.I. tract, and to avoid visual distortion caused by entrapped gas and adhesion of stool particles to the bowel wall, Laxsil with orange juice is clearly an improved method of preparing the G.I. tract for roentgenography.

*Marks, M. M. and Mason, W. E.: Improved Methods of Preparing the Gastrointestinal Tract for Roentgenography. *Abdominal Surgery, 14*:170, Sept. 1972.

an improved method of
evacuating stool and gas

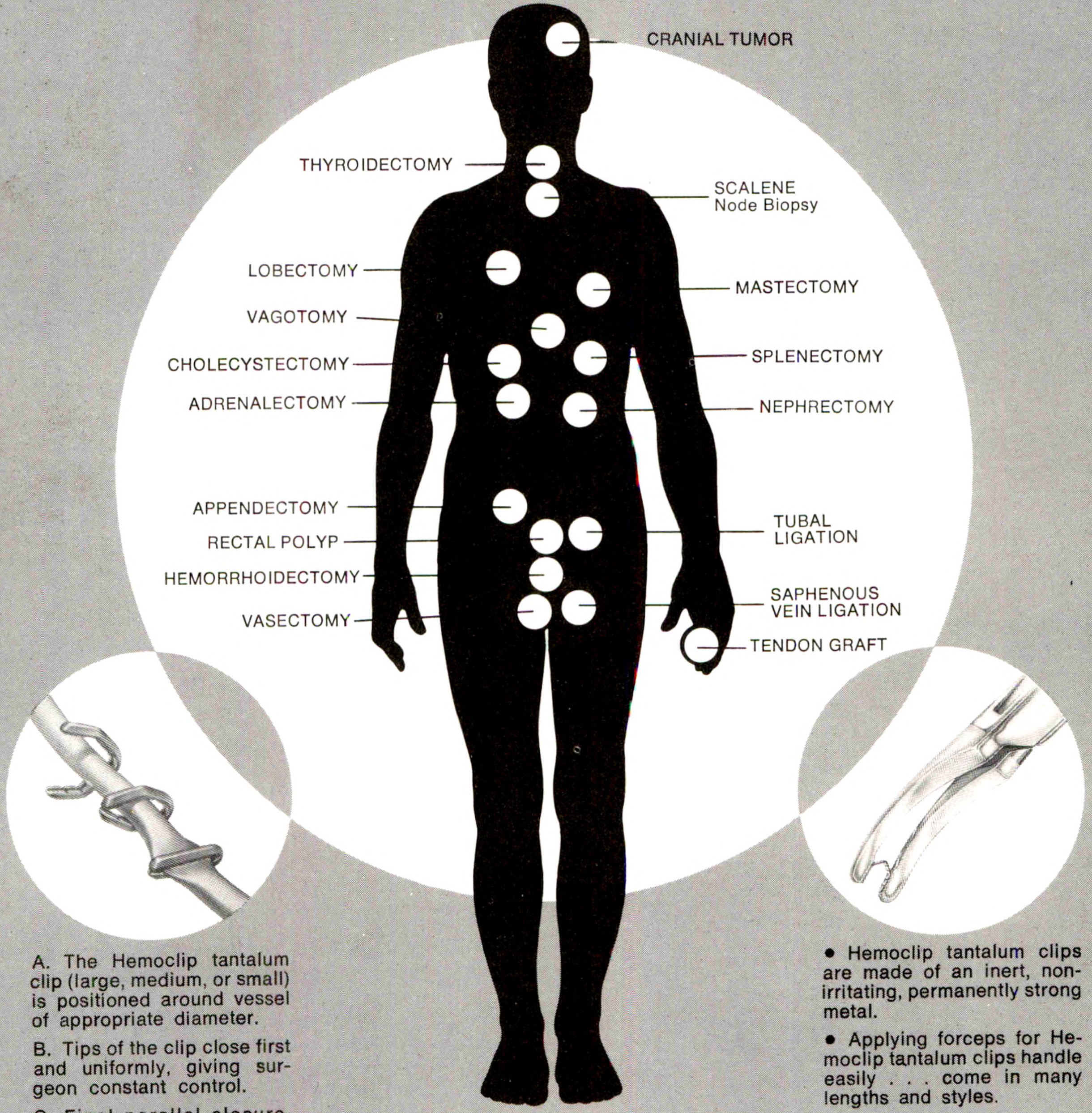
Laxsil® Liquid

Each tablespoon (15 ml.) contains 1.25 gm. magnesium hydroxide N.F. and 100 mg. activated simethicone in a pleasantly flavored liquid suspension. Available in 8 fl. oz. bottles.

HEMOCLIP®

TANTALUM CLIPS

Modern method of hemostasis, ideal in virtually all surgical procedures, proved quick and effective time and again in these specific operations:



A. The Hemoclip tantalum clip (large, medium, or small) is positioned around vessel of appropriate diameter.

B. Tips of the clip close first and uniformly, giving surgeon constant control.

C. Final parallel closure. Clip serrations grip tight on tissue.

- Hemoclip tantalum clips are made of an inert, non-irritating, permanently strong metal.
- Applying forceps for Hemoclip tantalum clips handle easily . . . come in many lengths and styles.

Please contact Department 003 for more detailed information.

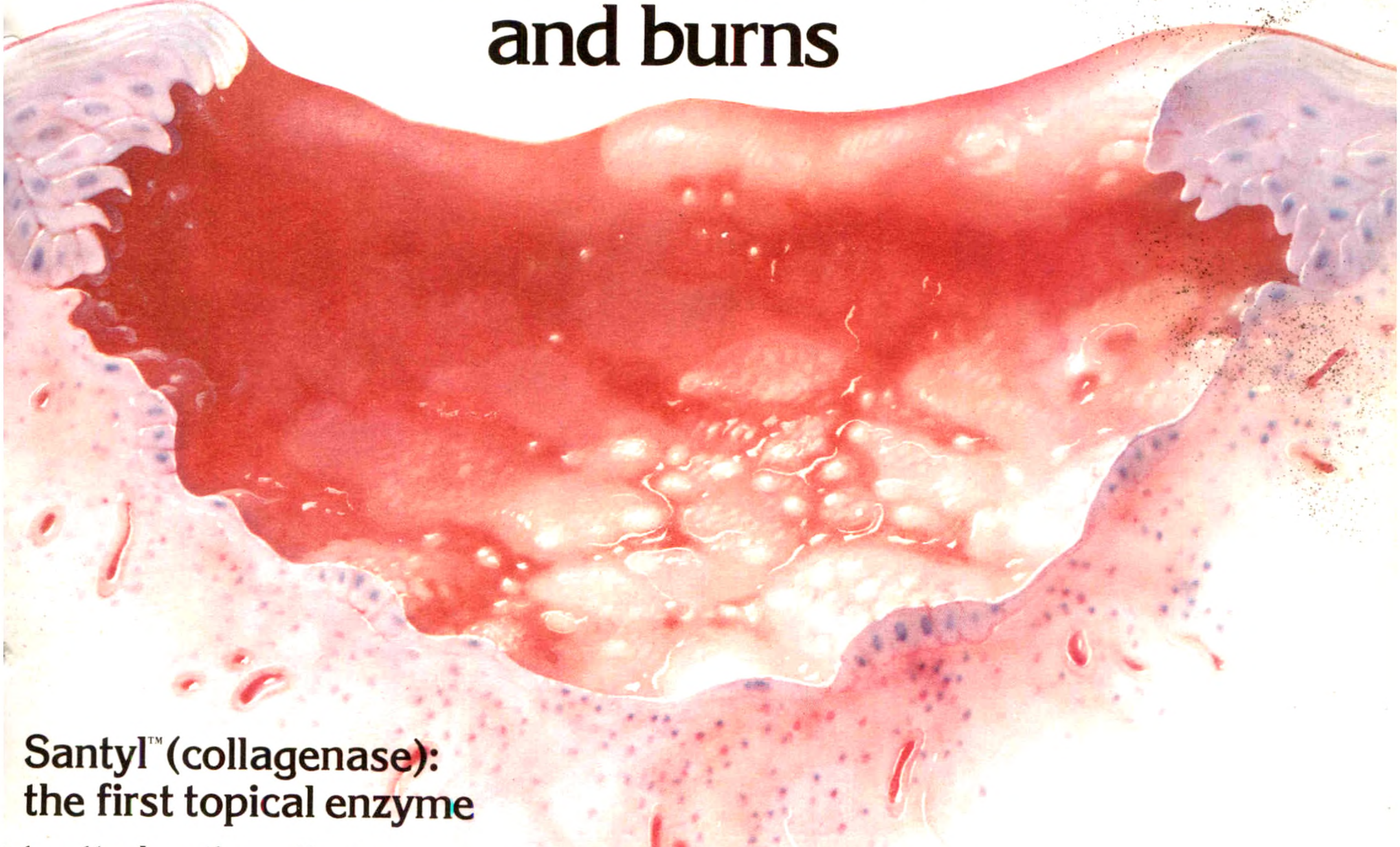
WECK®

EDWARD WECK & COMPANY, INC. • 49-33 31st Place, Long Island City, N.Y.11101

new Santyl™ ointment (collagenase)

digests debris and the collagen that anchors it

A better beginning for the treatment of dermal ulcers and burns



Santyl™ (collagenase): the first topical enzyme

- **to attack native collagen,** a substance ordinarily resistant to all common proteolytic enzymes used in wound debridement
- **to digest denatured collagen,** the main constituent of dense burn eschar and necrotic debris that must often be removed before healing can take place
- **to dissolve collagenous strands** that "anchor" debris to the wound surface

Please provide additional scientific information on Santyl ointment (collagenase)

Name 1 2 3 4 5 6

Nursing home affiliation

Hospital affiliation

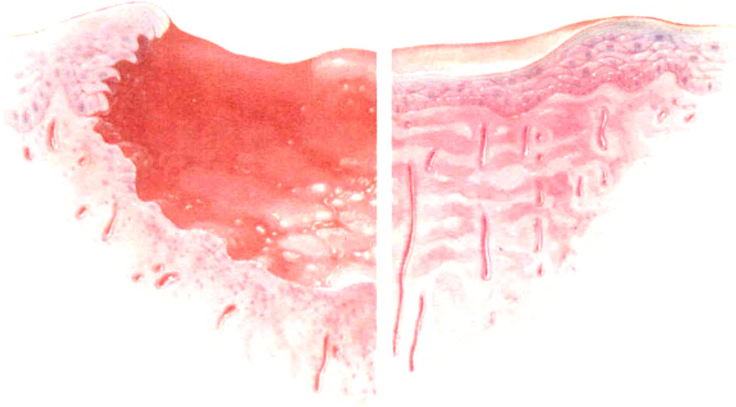
Office address

City State Zip code

Santyl™: new for dermal ulcers and burns

A cleaner base to build on promotes better healing in the end

Necrotic material is usually anchored to the wound surface by strands of undenatured collagen. Until these collagenous strands are severed, debridement is incomplete, granulation is slowed, and no supportive base is available for epithelization.[1]



Artist's conception of healing decubitus ulcer

With Santyl, debridement and subsequent healing have been reported to proceed rapidly.[1-3] A markedly reduced incidence of hypertrophic scarring reported with Santyl is believed to be due to the fact that epithelization proceeds from a completely debrided base.[1]

Indications: Santyl Ointment is indicated for debriding dermal ulcers and severely burned areas. In other types of necrotic skin lesions reports on the use of Santyl Ointment have been limited to clinical observations without controls. **Contraindications:** Application is contraindicated in patients who have shown local or systemic hypersensitivity to Collagenase.

Precautions: The enzyme's optimal pH range is 7 to 8. Lower pH conditions have a definite adverse effect on the enzyme's activity, and appropriate precautions should be taken.

The enzymatic activity is also adversely affected by detergents and hexachlorophene and heavy metal ions such as mercury and silver which are used in some antiseptics. When it is suspected such materials have been used, the site should be carefully cleansed by repeated washings with normal saline before Santyl Ointment is applied. Soaks containing metal ions or acidic solutions such as Burow's solution should be avoided because of the metal ion and low pH. Cleansing materials such as hydrogen peroxide or Dakin's solution do not interfere with the activity of the enzyme.

Debilitated patients should be closely monitored for systemic bacterial infections because of the theoretical possibility that debriding enzymes may increase the risk of bacteremia.

The ointment should be confined to the area of the lesion in order to avoid the risk of irritation or maceration of normal skin.

A slight erythema has been noted occasionally in the surrounding tissue particularly when the enzyme ointment was not confined to the lesion. This can be readily controlled by protecting the healthy skin with a material such as Lassar's paste.

Since the enzyme is a protein, sensitization may develop with prolonged use although none has been observed to date.

Adverse Reactions: Adverse reactions to Collagenase have not been noted when used as directed.

Dosage & Administration: Santyl Ointment should be applied once daily (or once every other day in the case of outpatients) in the following manner.

(1) Prior to application the lesions should be gently cleansed with a gauze pad saturated in normal saline, buffer (pH 7.0-7.5) or hydrogen peroxide to remove any film and digested material.

(2) Whenever infection is present, as evidenced by positive cultures, pus, inflammation or odor, it is desirable to use an appropriate topical antibacterial agent. Neomycin-Bacitracin-Polymyxin B (Neosporin) has been found compatible with Santyl Ointment. This antibiotic should be applied to the lesion in powder form or solution prior to the application of Santyl Ointment. Should the infection not respond, therapy with Santyl Ointment should be discontinued until remission of the infection.

(3) Santyl Ointment should be applied (using a wooden tongue depressor or spatula) directly to deep wounds, or, when dealing with shallow wounds, to a sterile gauze pad which is then applied to wound. The wound is covered with sterile gauze pad and secured with clear tape or Kling bandage.

(4) Crosshatching thick eschar with a #11 blade is helpful. It is also desirable to remove as much loosened detritus as can be done readily with forceps and scissors.

(5) All excess ointment should be removed each time dressing is changed.

(6) Use of the ointment should be terminated when sufficient debridement of necrotic tissue has taken place.

Overdose: Action of the enzyme may be stopped, should this be desired, by the application of Burow's solution U.S.P. (pH 3.6-4.4) to the lesion.

How Supplied: Santyl Ointment contains 250 units of Collagenase enzyme per gram of white petrolatum U.S.P. The potency assay of Collagenase is based on the digestion of undenatured collagen (from bovine Achilles tendon) at pH 7.2 and 37°C. for 24 hours. The number of peptides cleaved are measured by reaction with ninhydrin. Peptides released by a trypsin digestion control are subtracted. One net Collagenase unit will solubilize ninhydrin reactive material equivalent to 4 micromoles of Leucine.

1. Boxer A M *et al*: *Geriatrics*, July 1969. **2.** Haimovici H and Strauch B: in Mandl Ines (ed): Collagenase, Gordon and Breach, New York, 1972, p. 177. **3.** Bardfeld L A: *op cit*, p. 191. **4.** Varma A O *et al*: *Surg. Gynec. Obstet.* *136*:281, Feb. 1973.

A free in-service educational program on the use of Santyl will be provided upon request.

First Class
Permit No. 528
Clifton
New Jersey 07012

BUSINESS REPLY MAIL

No postage stamp necessary if mailed in the United States

Postage will be paid by

Knoll Pharmaceutical Co.
30 North Jefferson Road
Whippany, New Jersey
07981

Santyl™
ointment
(collagenase)

"...because of its unique ability to hydrolyze native collagen, it may prove to be the drug of choice for wound debridement."[4]

Knoll Pharmaceutical Co.
30 North Jefferson Road
Whippany, New Jersey
07981

Let Saunders sharpen your surgical skills –

SLEISENGER & FORDTRAN:

Gastrointestinal Disease

From heartburn to parasitic diseases, from hemorrhoids to carcinoid tumors—no gastrointestinal disturbance is neglected in this monumental volume. In 115 chapters, over 50 contributors offer documented techniques for diagnosis and management, incorporating the latest findings in *surgery, endoscopy, environmental factors*, and *pediatric disorders*.

Edited by Marvin H. Sleisenger, *M.D., Prof. and Vice Chairman, Dept. of Medicine, Univ. of Calif. School of Medicine, S.F.; and* John S. Fordtran, *M.D., Prof. of Medicine, Univ. of Texas Southwestern Medical School. About 1660 pp., 725 figs. About $35.00. August.*

KATZ & KADIS:

Anesthesia in Uncommon Diseases

A one-of-a-kind volume that relates anesthetic management to the pathophysiology of uncommon, though not necessarily rare entities. System by system, 25 contributors point out the precautions called for in managing patients with *phenylketonuria, septic shock, chronic pyelonephritis, pemphigus*—even environmental and behavioral disorders.

Edited by Jordan Katz, *M.D., Prof. and Assoc. Chairman, Dept. of Anesthesiology, Univ. of Wisconsin Medical School; and* Leslie B. Kadis, *M.D., Asst. Prof. of Anesthesia, Stanford Univ. School of Medicine. About 545 pp. Illustd. About $22.50. August.*

The Surgical Clinics of North America, August:

Surgery of the Chest

Philip E. Bernatz, *M.D., Guest Editor*

This month's issue pools the knowledge of 41 Mayo Clinic experts to bring you the latest insights into chest surgery. In 23 articles, you'll find clinically pertinent information on *lung cancer, diffuse pulmonary disease, operative respiratory care, anesthesia, tracheostomy in infants*, and much more—all typical of the hard-hitting symposia subscribers receive every other month.

Published bimonthly. Av. 275 pp. Illustd. Hardbound. No advertising. Available only by yearly subscription of six consecutive numbers, $21.00.

HENDERSON:

Orbital Tumors

Complete in one volume: the diagnosis, pathology and management of orbital tumors. The author covers 465 cases seen at The Mayo Clinic, describing surgical approaches and reporting follow-up on many. Important new data is presented on *inflammatory pseudotumors, secondary epithelial neoplasms*, and *intrinsic neoplasms of the lacrimal gland*.

By John W. Henderson, *M.D., Chairman, Dept. of Ophthalmology, Mayo Clinic. About 785 pp., 370 figs. About $40.00. August.*

YOUMANS:

Neurological Surgery

Comprehensive clinical guidance in all aspects of neurosurgery by over 100 eminent practitioners, researchers and educators. Features use of *echoencephalography in localizing tumors, advances in microoperative techniques, application of rostral cingulumotomy in cases of intractable pain, management for skull tumors, findings on parasitic brain infections*, and much more.

Edited by Julian T. Youmans, *M.D., Prof. and Chairman, Dept. of Neurosurgery, Univ. of Calif. at Davis. Three volumes. 2024 pp. 971 figs. $114.00. April.*

POPPEN:

Atlas of Neurosurgery

This classic text is being made available again as the perfect working companion to *Youmans*. 248 full-page plates with operative instructions show in step-by-step detail techniques ranging from *supraorbital neurectomy for trigeminal neuralgia*, through *craniotomy, to operations on peripheral nerves of the leg*. From incision to closure, it's a time-tested guide to proven methodology.

By James L. Poppen, *M.D., The Lahey Clinic. 522 pp. 248 plates. $35.00. 1960.*

W. B. SAUNDERS COMPANY

West Washington Square, Philadelphia, Pa. 19105

Please send and bill me:

☐ 8363 Sleisenger: *Gastro. Disease*—About $35.00

☐ 5299 Katz: *Anesthesia*—About $22.50

☐ Surgical Clinics starting August 1973—$21.00

☐ 4633 Henderson: *Orbital Tumors*—About $40.00

☐ 9655-7 Youmans: *Neurosurgery*—$114.00

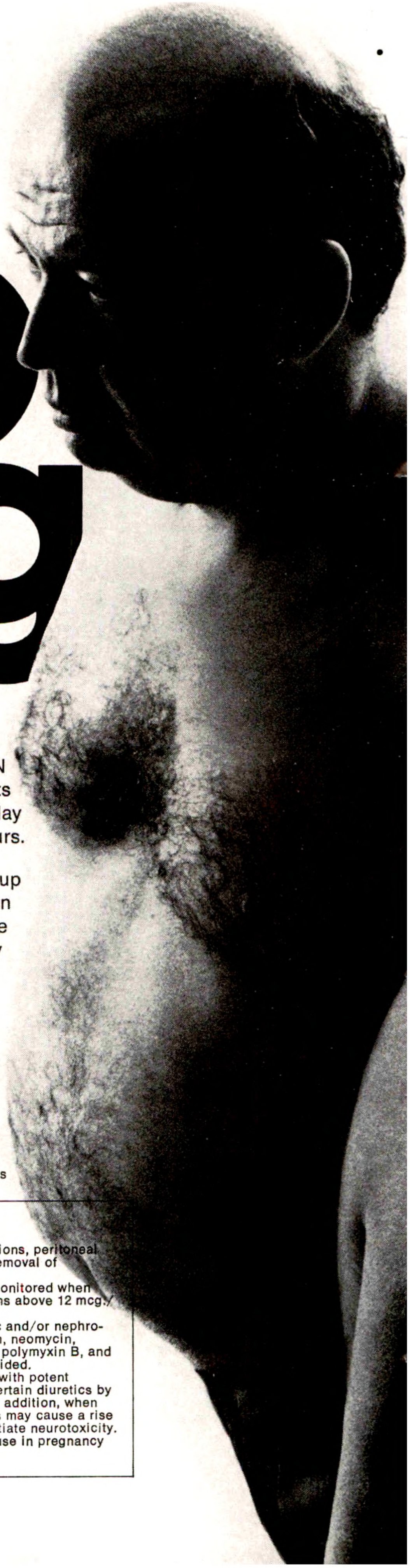
☐ 7290 Poppen: *Atlas of Neurosurgery*—$35.00

Name__________ Address__________

__________ Zip__________

AOS873

Simplified adult dosage guidelines in serious gram-negative infections...*



Over 132 lbs. **80 mg** q 8h.

The recommended dosage of GARAMYCIN Injectable for serious infections in patients with normal renal function is 3 mg./kg./day administered in three equal doses every 8 hours.

Life-Threatening Infections: Dosages of up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

*Due to susceptible organisms

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

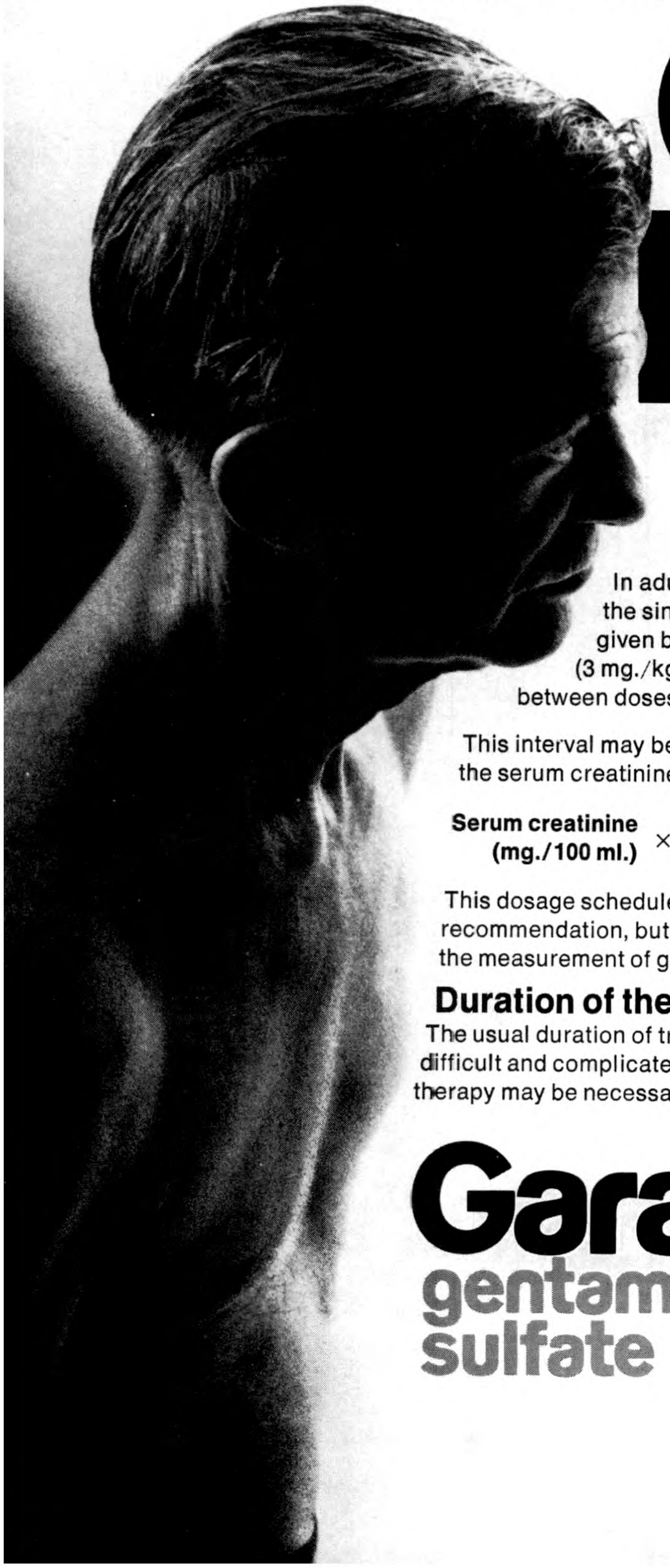
Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

COPYRIGHT ©1973, SCHERING CORPORATION. ALL RIGHTS RESERVED.

Schering



132 lbs. or less

60 mg.

q 8h.

In adults with impaired renal function, the single dose of GARAMYCIN Injectable given by patient weight remains the same (3 mg./kg./day); however, the interval between doses must be extended.

This interval may be approximated by multiplying the serum creatinine by 8 as follows:

$$\frac{\textbf{Serum creatinine}}{\textbf{(mg./100 ml.)}} \times 8 = \frac{\textbf{frequency of administration}}{\textbf{(in hours)}}$$

This dosage schedule is not intended as a rigid recommendation, but is provided as a guide to dosage when the measurement of gentamicin serum levels is not feasible.

Duration of therapy—7 to 10 days

The usual duration of treatment is 7 to 10 days. In difficult and complicated infections, a longer course of therapy may be necessary.

Garamycin®

gentamicin sulfate **injectable**

I.M./I.V.

40 mg. per ml.

Each ml. contains
gentamicin sulfate equivalent
to 40 mg. gentamicin

See Clinical Considerations section which follows

Schering

Over 132 lbs.
80 mg
q 8h.
132 lbs. or less
60 mg.
q 8h.

Simplified adult dosage guidelines for Garamycin®

gentamicin sulfate
injectable
I.M./I.V.

40 mg. per ml.
Each ml. contains gentamicin sulfate equivalent to 40 mg. gentamicin

GARAMYCIN® Injectable, brand of gentamicin sulfate U.S.P., injection, 40 mg. per ml.
Each ml. contains gentamicin sulfate equivalent to 40 mg. gentamicin
For Parenteral Administration

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, Proteus species (indole-positive and indole-negative), **Escherichia coli** and **Klebsiella-Enterobacter-Serratia** species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin type drug is usually indicated as concomitant antimicrobial therapy.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the rat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS:

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, thrombocytopenia, purpura; fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:

PATIENTS WITH NORMAL RENAL FUNCTION*

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lb.), the usual dosage is 80 mg. (2 ml.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

*In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration, in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 ml. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution in both instances should normally not exceed 1 mg./ml. (0.1%). The solution is infused over a period of 1 to 2 hours.

The recommended dose for intravenous administration is identical to that recommended for intramuscular use.

GARAMYCIN Injectable should not be physically premixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per ml., 2 ml. multiple-dose vials for parenteral administration.

Also available, GARAMYCIN Pediatric Injectable, 10 mg. per ml., 2 ml. multiple-dose vials for parenteral administration. MARCH 1973
016

AHFS Category 8:12.28

For more complete prescribing details, consult Package Insert or Physicians' Desk Reference. Schering literature is also available from your Schering Representative or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033. SLR-465

"Current abstracts are amplified and illuminated by comments of the members of the Editorial Board, based on their own clinical experiences as well as those of other recognized authorities" . . . just one of the reasons why Lippincott's

REVIEW OF
SURGERY

helps Resident (special rate only $11.00) and Veteran Surgeon alike to keep up with current progress, trends, and attitudes in all branches of surgery and the surgical specialties.

A true saver of precious reading time—from its detailed Contents Pages to its meaty reviews, and abstracts especially classified for reader convenience—a typical issue includes:

- Focus—several Reviews of timely or other special significance
- An original Report of major importance
- Twenty or more Abstracts with Commentary (and oft-times, rebuttal)
- Residents Corner—comprising Brief (1 to 3-page) Reports and Investigations
- In-depth Reviews of Current Books in Surgery

TO PUT THE BIMONTHLY REVIEW OF SURGERY AT YOUR FINGERTIPS NOW,

SUBSCRIBE TODAY . . .

J. B. LIPPINCOTT COMPANY, EAST WASHINGTON SQUARE, PHILADELPHIA, PA. 19105 A/S

Please enter my subscription to REVIEW OF SURGERY for 1 year (6 issues), at ☐ $15 (U.S. and Canada); ☐ $17 (all other countries); Resident Rate ☐ $11 (U.S. only; also note "year" of residency and Specialty ____________).

PLEASE PRINT

☐ Payment Enclosed.

Name ____________

☐ Charge my account.

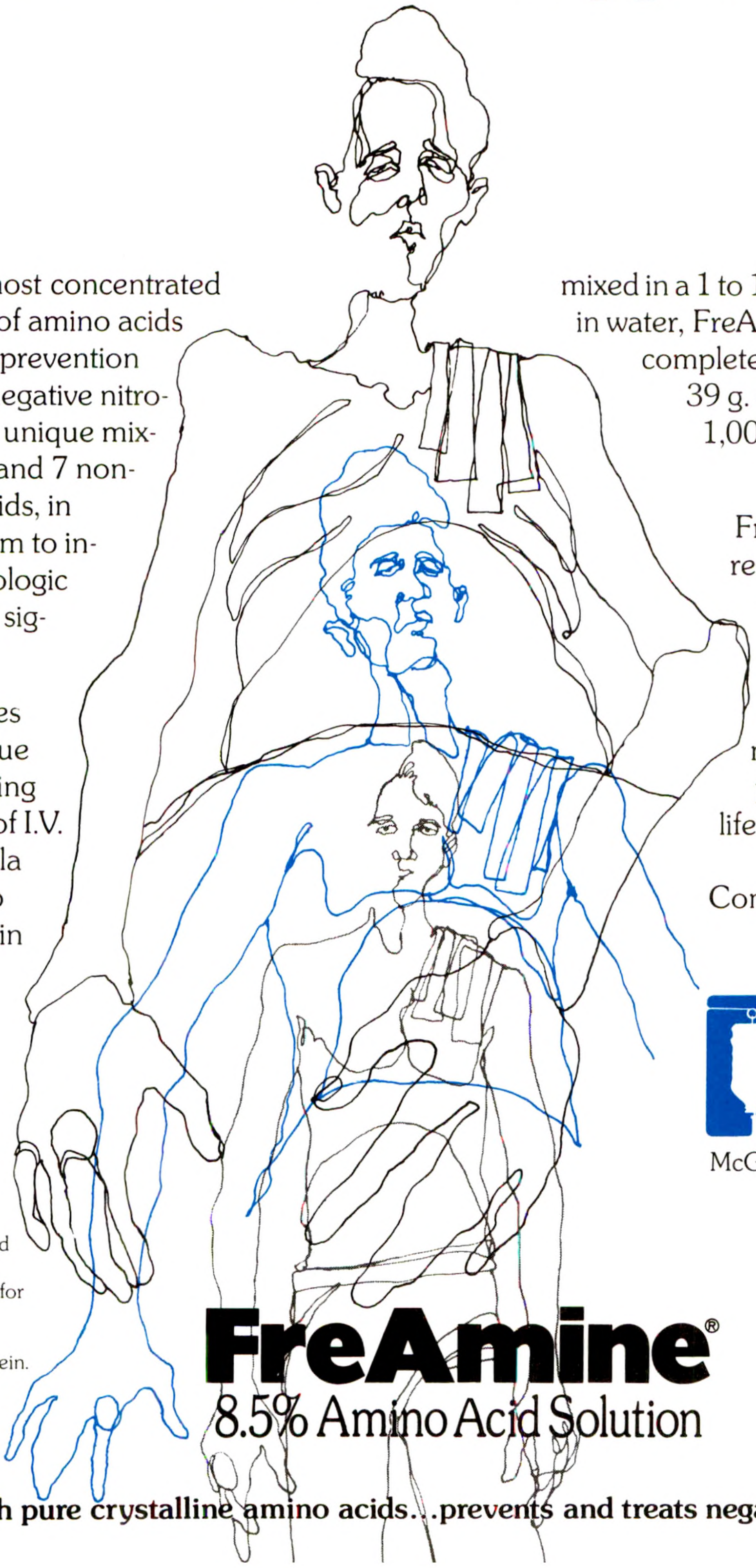
Address ____________

My Specialty is:

City/State/Zip ____________

____

When life hangs on protein intake... FreAmine® is life-supportive*



FreAmine is the most concentrated parenteral source of amino acids obtainable for the prevention and treatment of negative nitrogen balance. It is a unique mixture of 8 essential and 7 nonessential amino acids, in pure crystalline form to insure immediate biologic availability without significant waste.

FreAmine promotes anabolism and tissue synthesis even during extended periods of I.V. nutrition. Its formula is based on the two international protein standards. When mixed in a 1 to 1 ratio with 50% dextrose in water, FreAmine provides 6.25 g. of completely utilizable nitrogen and 39 g. of protein equivalent per 1,000 ml, plus 850 total nonprotein calories.

FreAmine is furnished in a ready-to-mix kit containing everything necessary for basic hyperalimentation, including 50% dextrose in water. Find out more about how McGaw puts it all together—with life-supporting I.V. nutrition in convenient kit form. Contact your McGaw representative or write for free brochure.

McGaw puts it all together.

*With adequate calories and other nutrients, when oral alimentation is not feasible for prolonged periods and/or there is impaired gastrointestinal absorption of protein.

FreAmine®

8.5% Amino Acid Solution

Supports life with pure crystalline amino acids...prevents and treats negative nitrogen balance.*

DESCRIPTION: Each 100 ml. contains: FreAmine Amino Acid Mixture*, 8.5 g; Sodium Bisulfite, U.S.P., less than 0.10 g.; Water for Injection, U.S.P. q.s., pH adjusted with acetic acid (approximately 20 mEq./l. Acetate).

Approximate concentration of amino acids (g./100 ml.):

Essential Amino Acids: L-Isoleucine 0.59; L-Leucine 0.77; L-Lysine HCl 0.77; Methionine 0.45; L-Phenylalanine 0.48; L-Threonine 0.34; L-Tryptophan 0.13; L-Valine 0.56.

Nonessential Amino Acids: L-Alanine 0.60; L-Arginine 0.31; L-Histidine 0.24; L-Proline 0.95; L-Serine 0.50; Aminoacetic Acid (Glycine) 1.8; L-Cysteine • HCl • H_2O <0.02. Alpha amino nitrogen greater than 80% of total nitrogen present. Concentration of Electrolytes (mEq./l.): Sodium 10, Chloride 45.

8.5% FreAmine Solution is a sterile, nonpyrogenic solution containing pure crystalline amino acids. A 500 ml. unit provides a total of 39 g. of protein equivalent and 6.25 g. of nitrogen.

ACTIONS: 8.5% FreAmine Solution provides, in concentrated form. a physiological ratio of completely utilizable amino acids for protein synthesis. Used with concentrated carbohydrate solutions, e.g., 20 to 50% dextrose solutions, as a source of calories plus electrolytes and vitamins, it provides total parenteral nutrition.

INDICATIONS: As an adjunct in the prevention of nitrogen loss, or in the treatment of negative nitrogen balance in patients where: (1) oral alimentation is not feasible for prolonged periods, and (2) there is impaired gastrointestinal absorption of protein.

CONTRAINDICATIONS: 1. Anuria. 2. Hepatic coma.

WARNINGS: Administration of amino acids to a patient with hepatic or renal insufficiency may result in a rise in blood ammonia or urea nitrogen. Rare instances of typically asymptomatic hyperammonemia have been reported in patients with no evidence of liver dysfunction receiving total parenteral nutrition. Since it appears dose-related, and more likely to develop in infants on prolonged total parenteral nutrition, conservative doses of amino acids should be given and blood ammonia periodically measured. If symptomatic hyperammonemia should develop, the nitrogen-containing solution should be discontinued and the patient's clinical status reevaluated.

The safe use of FreAmine in pregnant women has not been demonstrated.

PRECAUTIONS: It is essential to provide adequate calories for utilization of amino acids.

Hypertonic nutrient solutions should be administered through an indwelling intravenous catheter with the tip located in the superior vena cava.

HYPERALIMENTATION COMPLICATIONS: Potentially dangerous complications can be minimized by adherence to a careful protocol by an experienced team of pharmacist, nurse, and physician.

To prevent sepsis, rigid aseptic technique must be used in solution preparation and catheter placement and care.

The catheter dressing should be aseptically changed every 2-4 days and whenever contamination is suspected.

Consult clinical literature for discussion of management of sepsis during hyperalimentation.

The following metabolic complications have been reported: metabolic acidosis, hypophosphatemia, alkalosis, hyperglycemia and glycosuria, osmotic diuresis and dehydration, rebound hypoglycemia, elevated liver enzymes, and electrolyte imbalances. Frequent clinical evaluation and laboratory determinations are necessary to prevent or minimize these complications.

ADVERSE REACTIONS: Rare instances of hyperammonemia (see Warnings), and minor local reactions consisting of a warm sensation and erythema when FreAmine and hypertonic dextrose were administered by peripheral vein, have been reported.

DOSAGE AND ADMINISTRATION: Recommended Dietary Allowances of protein are approximately 0.9 g. per kilogram of body weight for a healthy adult and 1.4 to 2.2 g. per kilogram for healthy growing infants and children.** Requirements in trauma or malnutrition may be substantially increased. During hyperalimentation daily doses of approximately 1.0 to 1.5 g. per kilogram of body weight for adults and 2 to 3 g. per kilogram of body weight for infants are generally sufficient.

Calorie-to-nitrogen ratios of at least 100 to 150 nonprotein calories per gram of nitrogen have been recommended and may be provided by concentrated dextrose.

Sufficient vitamins, electrolytes, principally potassium, magnesium, and phosphate, as well as sodium, calcium, and chloride, must be given. Calcium and phosphate may be added to alternate infusate bottles to avoid precipitation, and sodium and potassium added as acetate or lactate salts to provide bicarbonate precursor. Serum electrolytes must be monitored frequently.

In adults, hypertonic mixtures may be safely administered only by continuous infusion through a central venous catheter with the tip located in the vena cava. 500 ml. of 8.5% FreAmine Solution, appropriately mixed with dextrose, electrolytes, and vitamins, is typically administered over an eight-hour period. Administration rate is governed by protein requirements and glucose tolerance. Advance dosage slowly with frequent determination of urine and blood sugar levels.

To prevent rebound hypoglycemia, 5% dextrose should be administered when hypertonic dextrose infusions are abruptly discontinued.

PEDIATRIC DOSAGE AND ADMINISTRATION: Small infants (up to 10 kg.) on total parenteral nutrition generally receive 2 to 3 g. of protein, 100 calories, and 120 to 150 ml. of fluid per kg. of body weight per day, provided in a solution of approximately 2⅛% FreAmine in 20% dextrose. Advance dosage slowly with frequent monitoring. (See Warnings above)

Large infants and children generally require 50 to 80 calories per kg. per day.

ROUTE: Intravenous.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

HOW SUPPLIED: 8.5% FreAmine Solution is supplied sterile and nonpyrogenic in 500 ml. intravenous infusion bottles.

*Crystalline amino acid mixture, isolated and purified from edible soybean hydrolysate or synthesized.

**500 ml. of 8.5% FreAmine Solution contains 6.25 g. of nitrogen, and the equivalent of 39 g. of protein.

McGAW LABORATORIES
Division of American Hospital Supply Corporation
Glendale, California • Milledgeville, Georgia

ARTERIAL SURGERY

By H. H. G. Eastcott, M.D., F.R.C.S.

This handsomely-illustrated work offers an exceptionally complete clinical, pathological and therapeutic presentation of the entire range of arterial disorders. The causes of arterial diseases and injuries are fully described, together with precise surgical procedures. The entire clinical picture for each disorder is discussed, and an abundance of case reports is included.

"Only a surgeon with a breadth and depth of experience could present the subject so thoroughly and authoritatively. . . . This is an outstanding volume which can be highly recommended and without reservation to medical students, residents, general surgeons, and, in this reviewer's opinion, to experienced vascular surgeons."—*Surgery, Gynecology and Obstetrics.*

412 Pages 652 Illustrations 1969 $22.00

J. B. Lippincott Company
East Washington Square
Philadelphia, Pa. 19105

Please send me:

Arterial Surgery $22.00

NAME ....

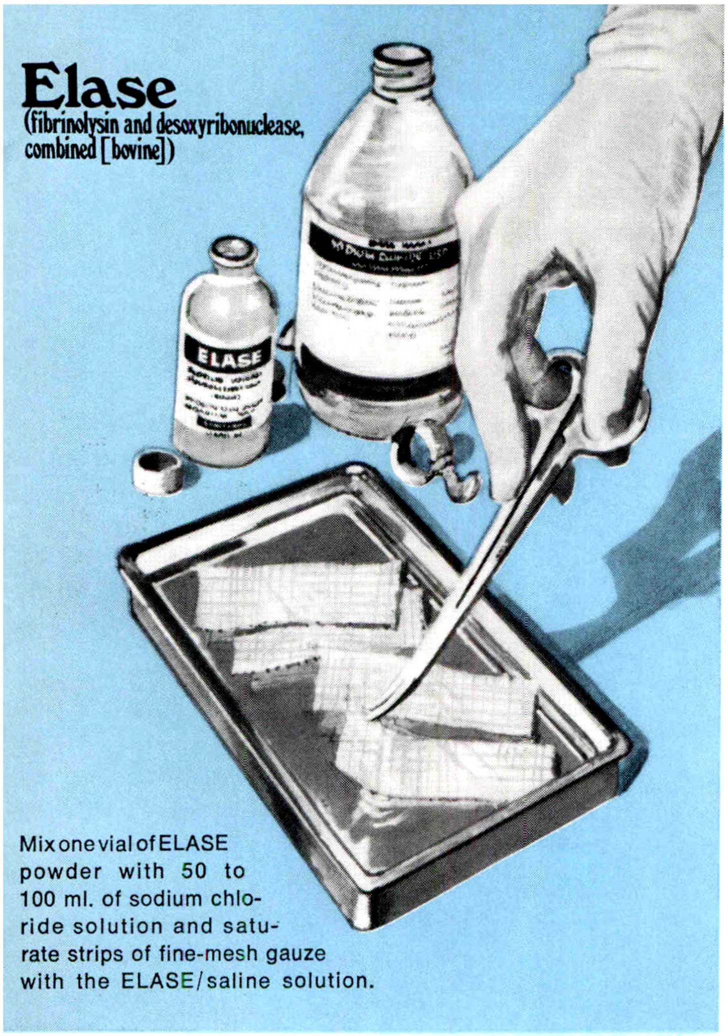
ADDRESS ....

CITY ....

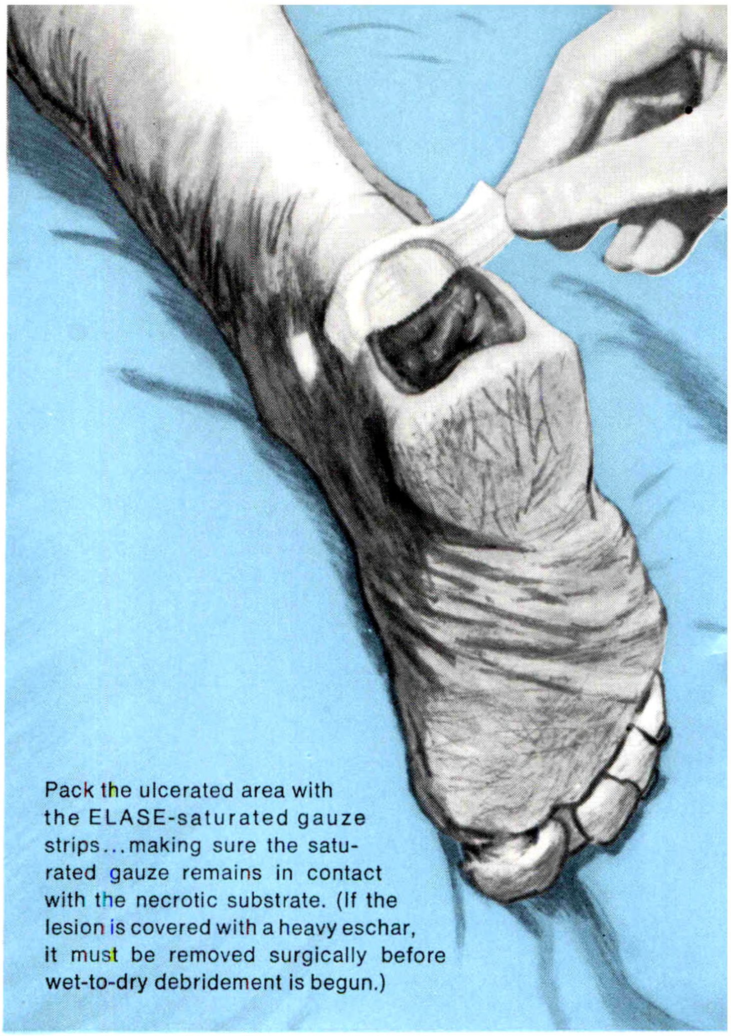
STATE .... Zip CODE ......

☐ Payment Enclosed ☐ Bill me AS 8/73

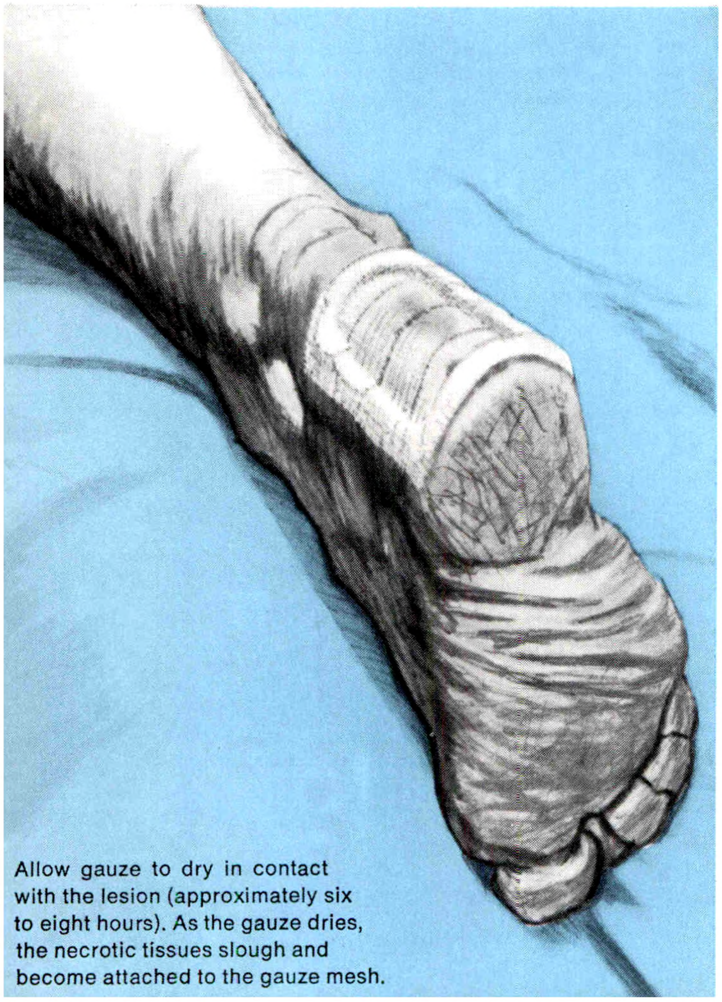
Elase
(fibrinolysin and desoxyribonuclease, combined [bovine])



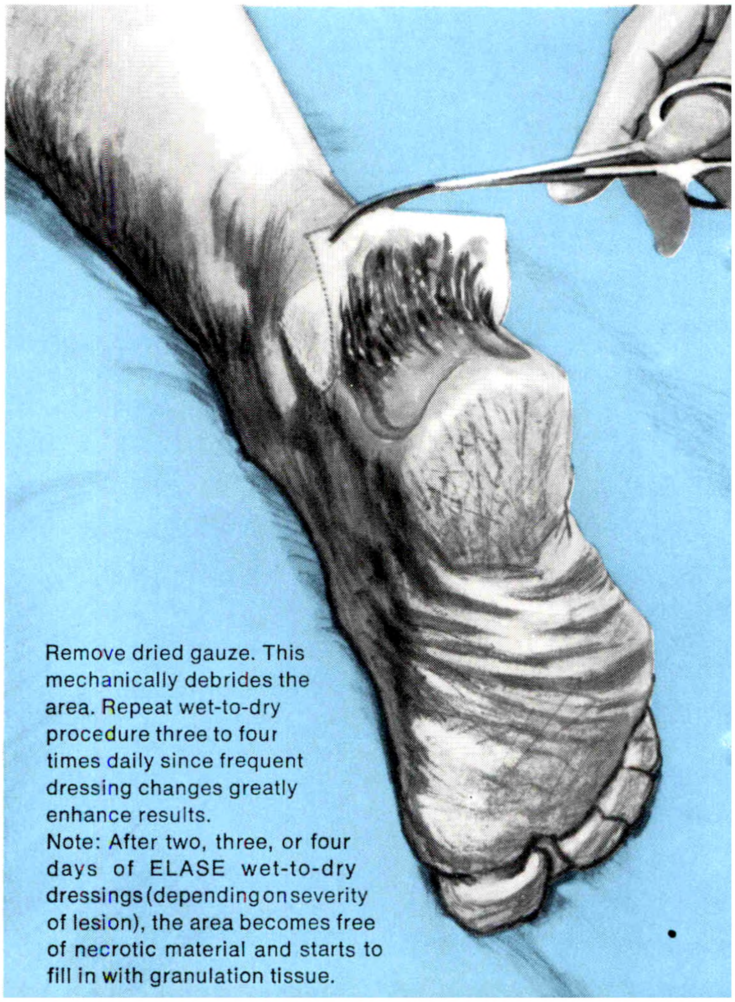
Mix one vial of ELASE powder with 50 to 100 ml. of sodium chloride solution and saturate strips of fine-mesh gauze with the ELASE/saline solution.



Pack the ulcerated area with the ELASE-saturated gauze strips... making sure the saturated gauze remains in contact with the necrotic substrate. (If the lesion is covered with a heavy eschar, it must be removed surgically before wet-to-dry debridement is begun.)



Allow gauze to dry in contact with the lesion (approximately six to eight hours). As the gauze dries, the necrotic tissues slough and become attached to the gauze mesh.



Remove dried gauze. This mechanically debrides the area. Repeat wet-to-dry procedure three to four times daily since frequent dressing changes greatly enhance results.

Note: After two, three, or four days of ELASE wet-to-dry dressings (depending on severity of lesion), the area becomes free of necrotic material and starts to fill in with granulation tissue.

the new way is wet-to-dry ...debridement with Elase® solution

(fibrinolysin and desoxyribonuclease, combined [bovine])

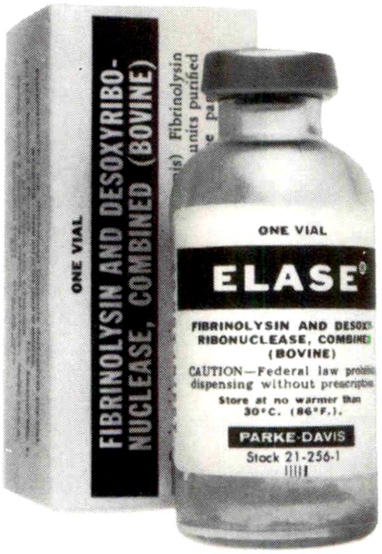
INDICATIONS: Elase is indicated for topical debridement in general surgical wounds, ulcerative lesions, burns, circumcision and episiotomy, and in cervicitis and vaginitis. Elase is used as an irrigating agent in infected wounds, otorhinolaryngologic wounds, and superficial hematomas (except when the hematoma is adjacent to or within adipose tissue).

CONTRAINDICATIONS: Elase is contraindicated in individuals with a history of hypersensitivity reactions to any of the components. Elase is not recommended for parenteral use since the bovine fibrinolysin may be antigenic.

PRECAUTIONS: The usual precautions against allergic reactions should be observed, particularly in persons with a history of sensitivity to materials of bovine origin or to mercury compounds.
To be maximally effective, Elase solutions must be freshly prepared before use. The loss in activity is reduced by refrigeration; however, even when stored in a refrigerator, the solution should not be used 24 hours or more after reconstitution.

ADVERSE REACTIONS: Side effects attributable to the enzymes have not been a problem at the dose and for the indications recommended. With higher concentrations, local hyperemia may be a side effect.

HOW SUPPLIED: Elase (powder) is supplied dried in 30-cc. rubber-diaphragm-capped vials containing 25 units (Loomis) of fibrinolysin and 15,000 units (modified Christensen method) of desoxyribonuclease with 0.1 mg. thimerosal (mercury derivative).
Elase Ointment is supplied in 30-Gm. tubes containing 30 units (Loomis) of fibrinolysin and 20,000 units of desoxyribonuclease with 0.12 mg. thimerosal and in 10-Gm. tubes containing 10 units of fibrinolysin and 6,666 units of desoxyribonuclease with 0.04 mg. thimerosal.



PARKE-DAVIS

Parke, Davis & Company, Detroit, Michigan 48232

HF PA 593 102171

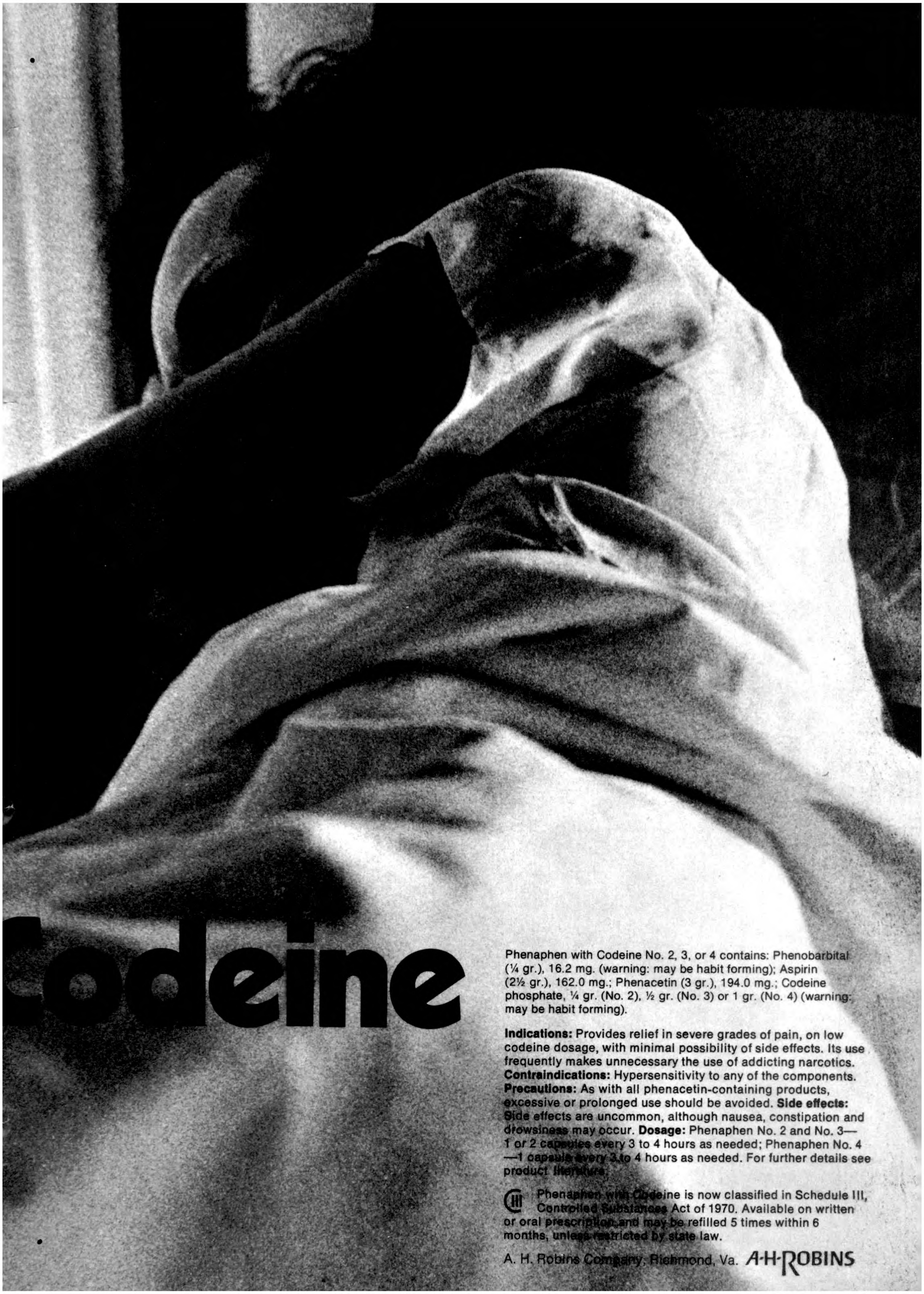
when pain goes on...
and on...
and on–

e analgesic formula that calms instead of caffeinates

Phenaphen® wit

or the patient with a terminal illness, PAIN past, present, and future can dominate s thoughts until it becomes almost an obsession. The more he is aware of the pain is now experiencing, the more difficult it is to erase his memory of yesterday's in, and to allay his fearful anticipation of tomorrow's pain.

rely the last thing this patient needs is an analgesic containing caffeine to stimulate e senses and heighten pain awareness. A far more logical choice is Phenaphen th Codeine. The sensible formula provides ¼ grain of phenobarbital to take e nervous "edge" off, so the rest of the formula can help control the pain more fectively. Don't you agree, Doctor, that psychic distress is an important factor most of your terminal and long-term convalescent patients?



Phenaphen with Codeine No. 2, 3, or 4 contains: Phenobarbital (¼ gr.), 16.2 mg. (warning: may be habit forming); Aspirin (2½ gr.), 162.0 mg.; Phenacetin (3 gr.), 194.0 mg.; Codeine phosphate, ¼ gr. (No. 2), ½ gr. (No. 3) or 1 gr. (No. 4) (warning: may be habit forming).

Indications: Provides relief in severe grades of pain, on low codeine dosage, with minimal possibility of side effects. Its use frequently makes unnecessary the use of addicting narcotics. **Contraindications:** Hypersensitivity to any of the components. **Precautions:** As with all phenacetin-containing products, excessive or prolonged use should be avoided. **Side effects:** Side effects are uncommon, although nausea, constipation and drowsiness may occur. **Dosage:** Phenaphen No. 2 and No. 3—1 or 2 capsules every 3 to 4 hours as needed; Phenaphen No. 4—1 capsule every 3 to 4 hours as needed. For further details see product literature.

Ⓒ III Phenaphen with Codeine is now classified in Schedule III, Controlled Substances Act of 1970. Available on written or oral prescription and may be refilled 5 times within 6 months, unless restricted by state law.

A. H. Robins Company, Richmond, Va. A·H·ROBINS

BETADINE®

Chosen by NASA for Apollo

When potential moon germs were a threat NASA had selected a broad-spectrum BETADINE microbicide for decontamination of the lunar capsules in Apollo 11/12/14 splashdowns.

Now NASA again selects a BETADINE microbicide for environmental protection of Skylab astronauts against infection. BETADINE Solution is circling the earth in orbit, to be used regularly for disinfection of certain equipment and for contingencies.

Chosen by NASA

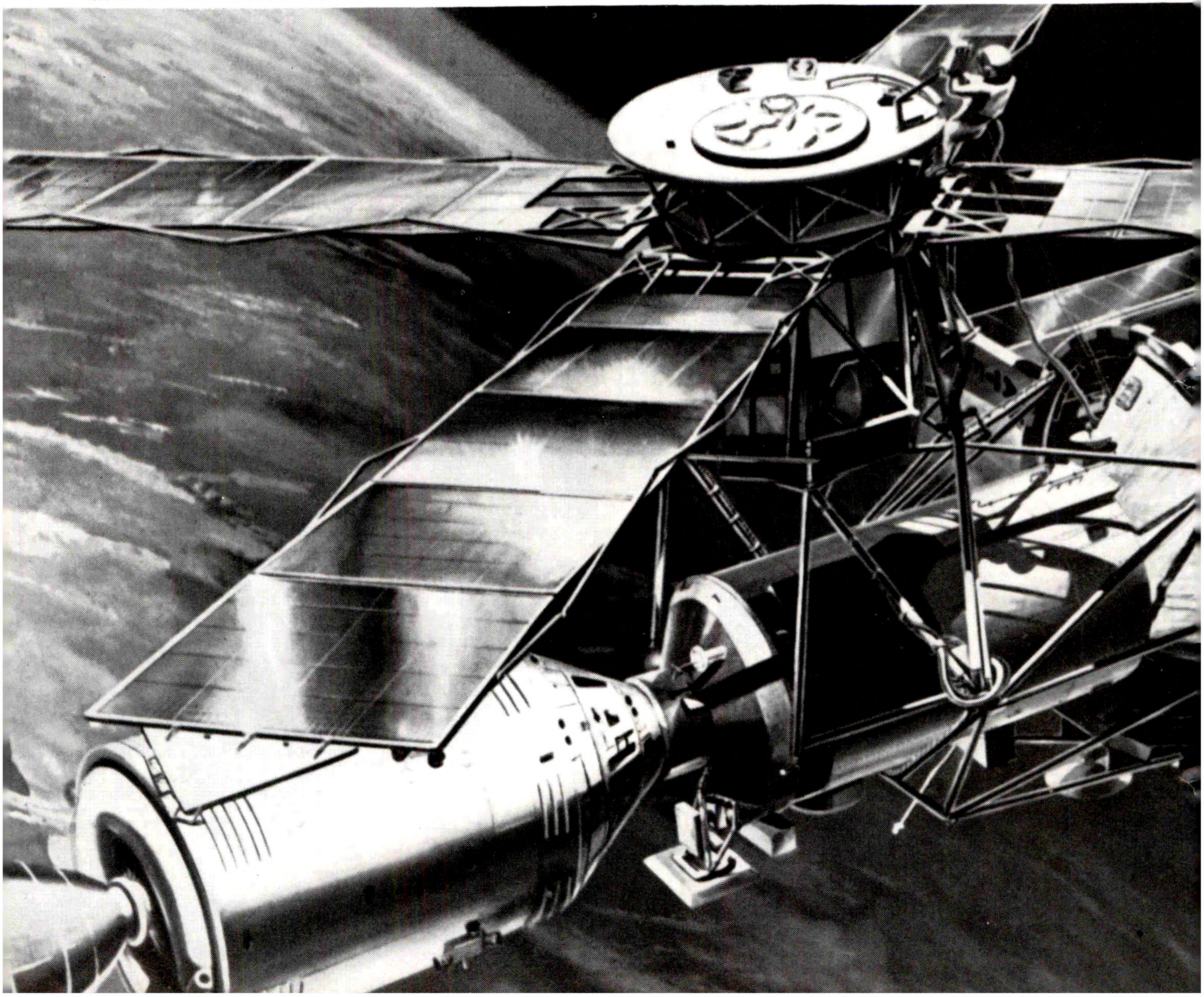
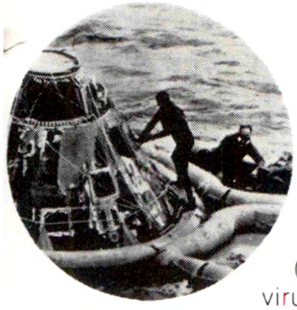


ILLUSTRATION: ARTIST'S CONCEPT OF SKYLAB IN ORBIT. COURTESY OF THE NATIONAL AERONAUTICS AND SPACE ADMINISTRATION.

Microbicides



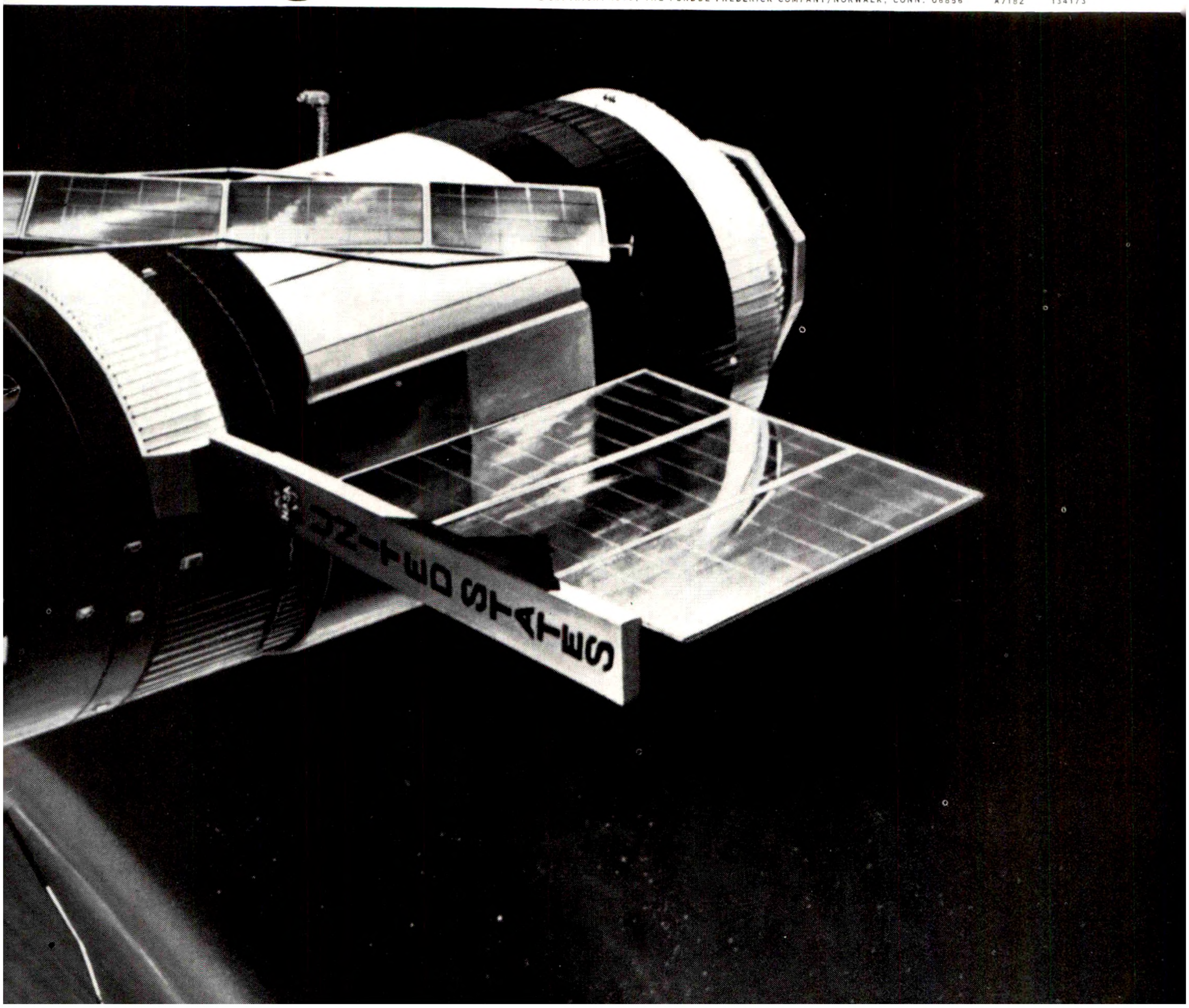
splashdowns!

Sky-high microbicidal efficacy plus down-to-earth convenience distinguishes BETADINE antiseptics. They *kill* bacteria (gram-positive and gram-negative), fungi, viruses, protozoa and yeasts. Yet they are virtually nonstinging, nonirritating and do not stain skin, mucosa, or natural fabrics. And they are available in a variety of forms, designed and formulated for specific uses.

Purdue Frederick

for Skylab mission!

©COPYRIGHT 1973, THE PURDUE FREDERICK COMPANY/NORWALK, CONN. 06856 A7182 134173



The controversial adenoma

One of the most common lesions of the GI tract. Often asymptomatic. Often an indication of the presence and/or development of more polyps. It has a much-debated relationship to colonic cancer. Some think it actually degenerates into a carcinoma. Some think not. When polyps are present in the distal colon, the best way to find them is through conventional sigmoidoscopic examination. And, be they benign or malignant, the best therapy is removal.

Many surgical procedures can contribute to temporary postoperative constipation. To help return bowel function to normal as quickly and as gently as possible, consider FLEET ENEMA for postoperative constipation relief.

- ■ Works rapidly, usually within 2 to 5 minutes
- ■ Cleanses the left colon and rectum; spares upper portions of the GI tract
- ■ Ready to use, easy to use, completely disposable
- ■ Unique construction regulates flow; prevents leakage and reflux
- ■ Anatomically correct, prelubricated rectal tip helps avoid injury to bowel wall

Fleet® Enema

Fast, effective relief of postoperative constipation

Contraindications: Do not use when nausea, vomiting, or abdominal pain is present. **Warnings:** Frequent or prolonged use of enemas may result in dependence. Take only when needed or when prescribed by a physician. **Precautions:** Do not administer to children under two years of age unless directed by a physician.

FREE BOOKLET. A supply of a patient booklet, *Protecting Yourself with a "Procto" Examination,* is available, free of charge, on request to C. B. FLEET CO., INC., P. O. Box 1100, Lynchburg, Va. 24505.

Fleet® pharmaceuticals

C. B. FLEET CO., INC.
Lynchburg, Va. 24505

Artist's conception.

F3A73

You can be there...

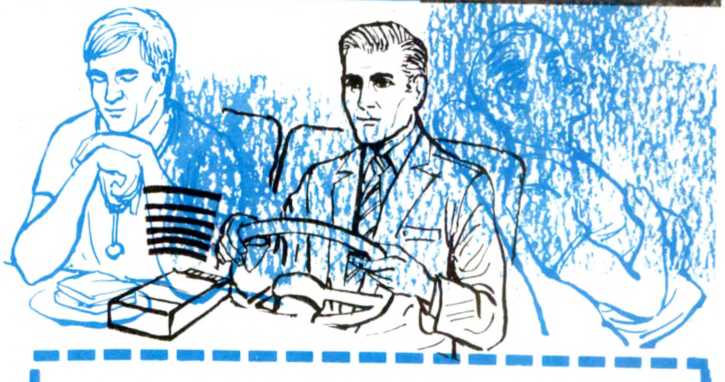
ACS/Clinitapes®

ACS/Clinitapes
Hiatus Hernia and Reflux Esophagitis
SIDE 1
C72-GS1
(Panel) Edward R Woodward, M.D., F.A.C.S. Gainesville

You can be there . . . at the 1973 Clinical Congress of the American College of Surgeons . . . sitting in on key sessions . . . Panels, Symposiums, Post-graduate Courses . . . all through the medium of ACS/CLINITAPES — exclusive, authoritative sound recordings.

Introduced in 1972, this new audio-cassette recording service of the American College of Surgeons helps keep you informed and up-to-date . . . in the privacy of your office . . . car . . . or home. You hear actual programs from this year's Spring Meeting and Clinical Congress . . . recorded live and reproduced in high quality cassettes. You add to your personal program of continuing surgical education with ACS/Clinitapes . . . the way to stay aware of new developments and advances in surgery . . . information vital to the busy professional.

Find out more about ACS/CLINITAPES **now** . . . the only cassette program where **you** choose the titles. Mail the convenient coupon **today.** No obligation.



AA

To: **ACS/Clinitapes**

55 EAST ERIE STREET • CHICAGO, ILLINOIS 60611

I am interested in more details on ACS/Clinitapes. Please send me, without obligation, information and current titles as soon as available.

Name______________________________

Street Address________________________

City______________ State________ Zip_______

RX FOR

Post Anorectal Surgery* —Tucks® medicated Pads.

SOOTHE WITHOUT SENSITIZING

Tucks pads soothe and comfort two ways after anorectal surgery, with no potentially sensitizing "caine" type anesthetic. As a wipe, these soft cotton flannel pads gently, yet thoroughly cleanse as they soothe. As a cooling compress they relieve post-operative discomforts. And they can be used as often as needed with minimum risk of sensitization or over-treatment.

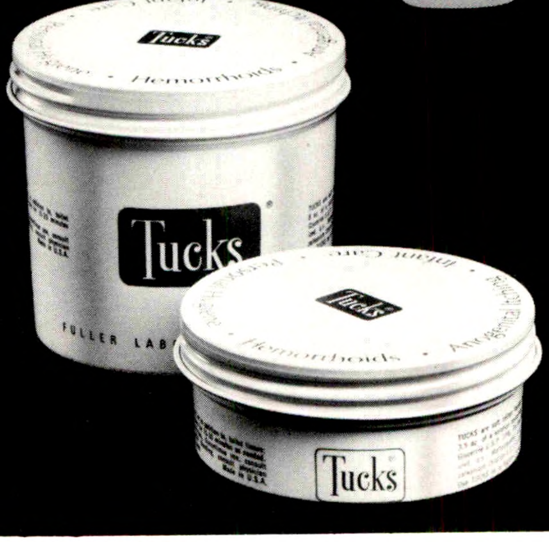
The solution is 50% witch hazel and 10% glycerine, buffered to pH 4.6 to maintain the natural skin acid level.

Trust Tucks for prompt relief of post-operative discomforts. And let your patients use them often. Send for a trial clinical supply on your Rx.

*The Committee on Pre and Postoperative Care, American College of Surgeons. Manual of Preoperative and Postoperative Care, Second Edition. W. B. Saunders Co., Philadelphia, Pa. 1971, p. 423

FULLER LABORATORIES, INC.
Eden Prairie, Minnesota 55343

fuller®



ATLAS of GASTROINTESTINAL SURGERY

KOMEI NAKAYAMA, M.D., Professor of Surgery, and Director of Institute of Gastroenterology, Tokyo Women's Medical College

Here is an atlas of exceptional surgical merit and surpassing beauty from a distinguished Japanese surgeon. Dr. Nakayama presents, in vivid, step-by-step fashion the surgical methods that have won him international acclaim.

The author is a pioneer and a world leader in the field of esophageal surgery. *One-third of his atlas is devoted to surgery of this type.* It includes a description, in minute detail, of Dr. Nakayama's reconstruction of the cervical esophagus using a revascularized segment of the bowel. In the remaining two-thirds of the atlas you'll find operations on the rest of the gastrointestinal tract plus the gall bladder, bile duct, liver, pancreas, and spleen.

Surgical indications, pre- and postoperative care, and complications are described along with the surgical techniques. A beautiful section of the atlas contains large photographs of, and instructions for the use of, Dr. Nakayama's instruments for small vessel anastomosis.

649 Pages 1500 Illustrations 1969 $42.00

J. B. Lippincott Company
East Washington Square
Philadelphia, Pa. 19105

Please send me:
Atlas of Gastrointestinal Surgery...... $42.00

NAME ....

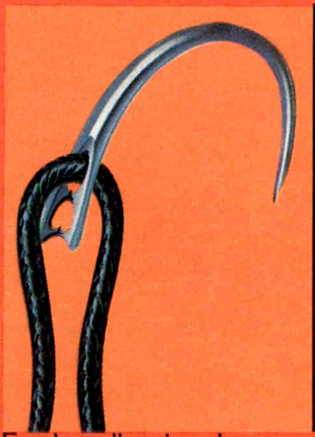
ADDRESS ....

CITY ....

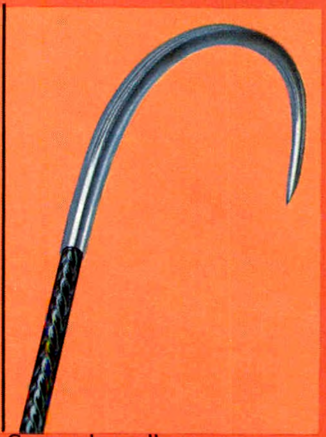
STATE .... Zip CODE ......

AS 8/73

Quicker than the eye...

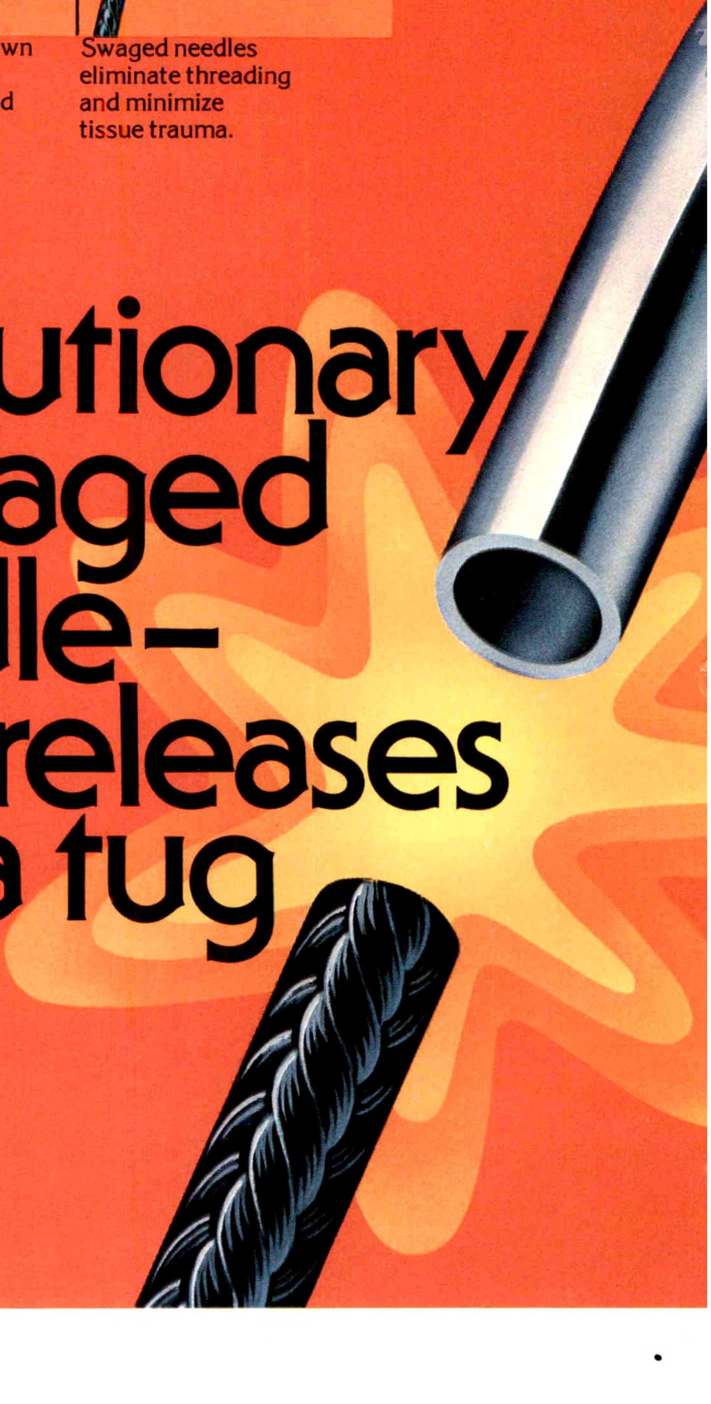


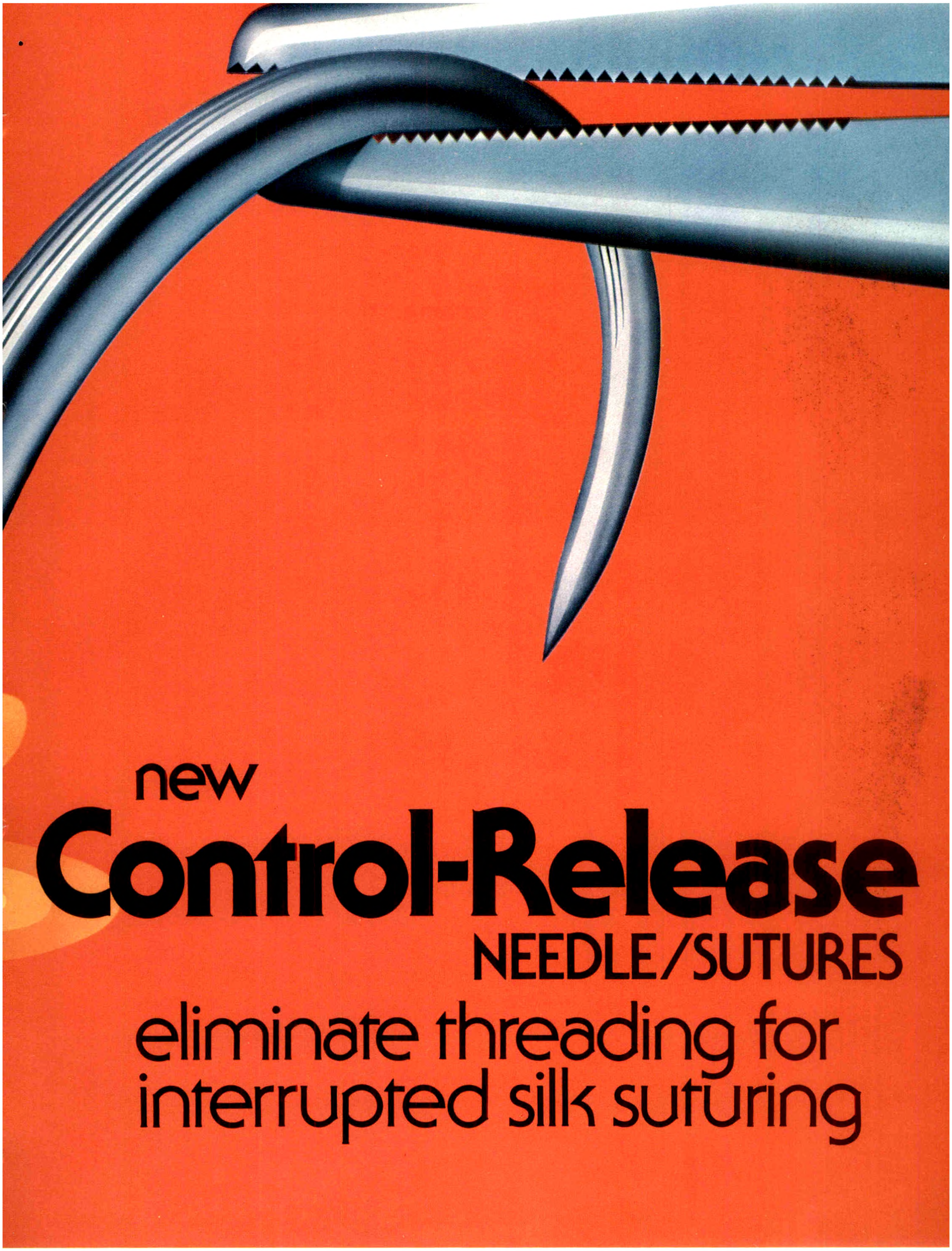
Eyed needles slow down
suture preparation
and increase likelihood
of tissue trauma.



Swaged needles
eliminate threading
and minimize
tissue trauma.

Revolutionary swaged needle–releases with a tug





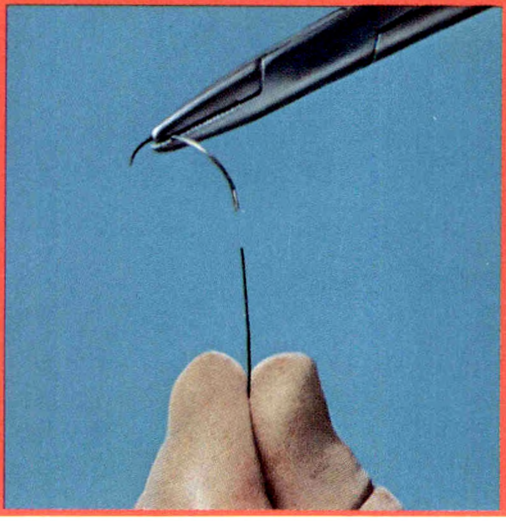
ETHICON Leadership in Wound Repair

Quicker than the eye

new
Control-Release
NEEDLE/SUTURES

For GI anastomosis and fascia closure

Reduced trauma. New, sharp, swaged needle with each suture. Helps provide leakproof anastomoses.

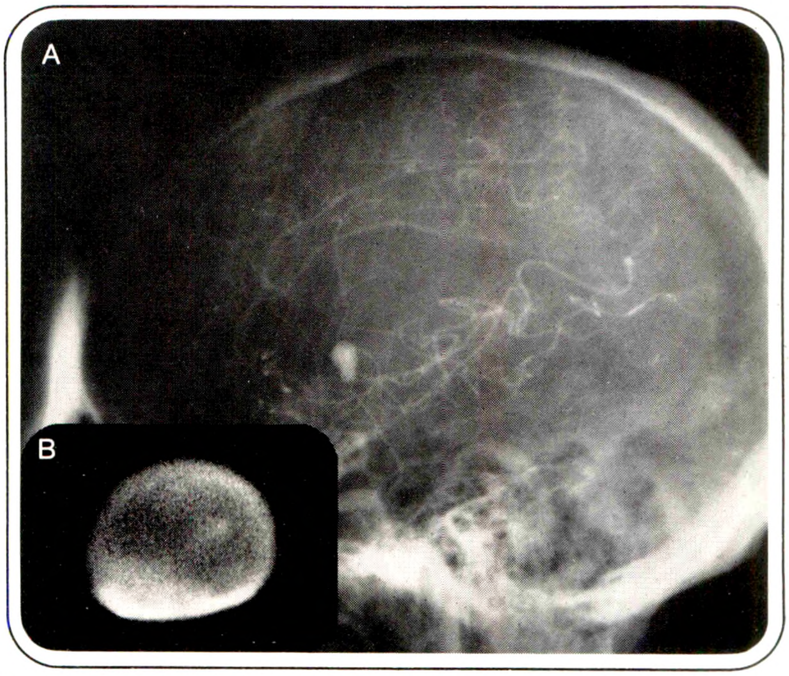


Faster. Needle releases with a tug—eliminates need for scissors.

ETHICON Leadership in Wound Repair

©ETHICON, INC. 1973 340677

brain abscess
or tumor*?



In any case...
when nutritional
supplementation
is indicated
after surgery

Berocca® is therapy
tablets

With balanced, high potency B-complex and C vitamins... No odor... Virtually no aftertaste... Lowest priced Rx formula.

Please see complete product information, a summary of which follows:

Each Berocca Tablet contains:

Thiamine mononitrate (Vitamin B_1)	15 mg
Riboflavin (Vitamin B_2)	15 mg
Pyridoxine HCl (Vitamin B_6)	5 mg
Niacinamide	100 mg
Calcium pantothenate	20 mg
Cyanocobalamin (Vitamin B_{12})	5 mcg
Folic acid	0.5 mg
Ascorbic acid (Vitamin C)	500 mg

Indications: Nutritional supplementation in conditions in which water-soluble vitamins are required prophylactically or therapeutically.

Warning: Not intended for treatment of pernicious anemia or other primary or secondary anemias. Neurologic involvement may develop or progress, despite temporary remission of anemia, in patients with pernicious anemia who receive more than 0.1 mg of folic acid per day and who are inadequately treated with vitamin B_{12}.

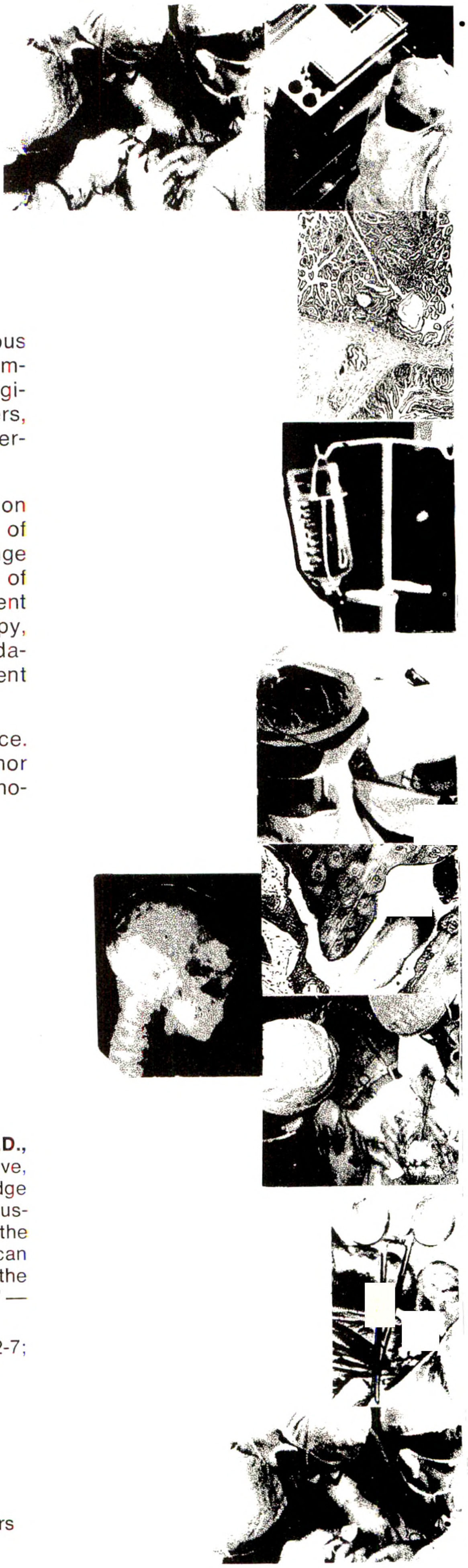
Dosage: 1 or 2 tablets daily, as indicated by clinical need.

Available: In bottles of 100 and 500.

ROCHE

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

*(A) Lateral arteriogram demonstrates depression of the middle cerebral group of vessels with absence of some of the ascending branches of the middle cerebral. A mycotic aneurysm is seen coming off one of the middle cerebral branches. (B) Lateral perfusion brain scan demonstrates an area of increased uptake in the parietal region. The patient has extensive infected encephalomalacia secondary to infarcted emboli from bacterial endocarditis. Any lesion altering the blood-brain barrier may give an increased pickup on brain scan.



Readings in
MODERN SURGERY

Edited by Richard H. Egdahl, M.D.
and John A. Mannick, M.D.

Inspired by the enthusiasm generated by their previous volume *Modern Surgery* (1970), the editors have compiled a second collection of the choice articles of surgical literature. With the exception of two classic papers, the articles presented are entirely new, as are the overviews and the annotated bibliographies.

The book's purpose is to focus the reader's attention on the best new articles dealing with those areas of clinical surgery in which there has been recent change or movement. This change might be the introduction of new operative techniques or other modalities of patient therapy, the critical re-evaluation of established therapy, or an updating of results of surgery with recommendations for future alterations in technique or patient management.

The format is designed for clarity and easy reference. The selected article is brought up-to-date by the author in the "overview" which follows each article. An annotated bibliography follows each overview.
April 1973, 688 pp., illus.
Hardcover, $21.50 ISBN 0-8089-0763-8;
Softcover, $14.50 ISBN 0-8089-0803-0

Core Textbook of Surgery

Edited by Richard H. Egdahl, M.D., John A. Mannick, M.D., and Lester F. Williams, Jr., M.D. Innovative, comprehensive, and up-to-date, this text embodies both the latest knowledge in surgery and the new priorities of medical education. Focusing on "core surgical principles" and problem solving, the editors have designed a book of essential information. "It can be confidently predicted that this book will rapidly win the respect and admiration of students and teachers alike."—
NEW ENGLAND J. MED.
June 1972, 480 pp., Softcover, $8.75 ISBN 0-8089-0772-7; Hardcover, $14.50 ISBN 0-8089-0762-X

GRUNE & STRATTON, INC.
A subsidiary of Harcourt Brace Jovanovich, Publishers
111 Fifth Avenue, New York, N.Y. 10003

Vascular Injury in Vietnam Combat Casualties:

Results of Treatment at the 24th Evacuation Hospital 1 July 1967 to 12 August 1969

J. JUDSON MCNAMARA, M.D.,* DONALD K. BRIEF, M.D.,*
WYATT BEASLEY, M.D.,* JOHN K. WRIGHT, M.D.*

From the Department of Surgery, University of Hawaii School of Medicine and Queen's Medical Center, Honolulu, Hawaii

THE MANAGEMENT of vascular disease in general has been greatly improved by experience gained in the treatment of acute arterial injuries resulting from war wounds. During the armed conflict in Vietnam a registry of vascular injuries has been maintained which has provided a broad summation of the types of injuries seen, the methods of surgical management of these injuries and the results of treatment.

The present report concerns a group of patients seen at one evacuation hospital in Vietnam (24th) over a 2-year period. The report is unique in that it represents a fairly extensive experience at only one hospital, thus providing better standardization of methods of management. Only a small number of surgeons (14) treated the majority of the injuries. Interestingly, the information is comparable to the overall Vietnam experience as reported by the vascular registry.[4] The one major exception is with popliteal arterial injury in which the present series is significantly better than the registry as a whole. This group of patients is examined in greater depth in an effort to determine which changes in treatment may have been responsible for the observed difference.

Patient Material:

Two hundred seventy-five patients with peripheral vascular injuries were treated at the 24th Evacuation Hospital from 1 July 1967 to 12 August 1969. All American service personnel were male. There were four Vietnamese women. Mean age for the entire group was 23.8 years. A vascular injury sheet was compiled on each patient (Fig. 1). Arterial repair was judged successful if the extremity survived with a normal distal pulse. A viable extremity with absent distal pulses was judged a failure. Amputation with or without distal pulses was also judged a failure. A few other failures were accounted for by the necessity of late ligation of an initially successful repair because of acute hemorrhage from the anastomosis. Patients who died less than 48 hours after injury were not included in the data. Patients surviving longer than 48 hours were then tabulated as to final status of their repair at the time of their discharge or death.

Results

General information on the group as a whole (Table 1) indicates that in the total group of 275 repairs there were 36 failures (13.1%). Amputation rate is considerably lower: 18 patients (6.5%). The amputation rates of 12.1% for popliteal injury is considerably better than previously reported and is discussed in more detail below. Success rate did not alter significantly between American servicemen (Table 2) and Free World Military Forces (primarily Vietnamese) (Table 3). However, the amputation rate, for Free World Military Forces was considerably lower. Venous grafts (usually saphenous vein) were utilized in about 40% of all injuries. Primary end-to-end repair

---

Submitted for publication May 8, 1972.

* Present Address: J. Judson McNamara, M.D., Honolulu, Hawaii.

Donald K. Brief, M.D. Newark Beth Israel Medical Center, Newark, New Jersey.

Wyatt Beasley, M.D., Medical College of Virginia, Richmond, Virginia.

John K. Wright, M.D., Nashville, Tennessee.

TABLE 1. *24th Evac Hospital 1 July 67–12 August 69* (All Patients)

Vessel	Cases	Vein Grafts	Post-op Pulses	Amputation #	Amputation %	Failures #	Failures %
Carotid	31						
Common	21	5	18	—	—	2	9.5
Internal	10	0	5	—	—	5	50.0
Aorta	3	0	3	0	0	0	0
Axillary	17	4	17	0	0	0	0
Brachial	75	35	71	2	2.7	4	5.3
Iliac	9	2	9	0	0	0	0
Common Femoral	5	2	4	0	0	1	20.0
Superficial femoral	77	39	66	9	11.7	11	14.3
Popliteal	59	28	45	7	11.9	13	22.4
Totals	276	115	238	18	6.5	36	13.1

Extremity Vascular Injuries

20/26 Failures associated with comminuted fractures

15/18 Amputations had vein grafts

8/9 Amputations in superficial femoral group and the one amputation in brachial group were secondary to hemorrhage

6 Patients requiring amputation had patent grafts at time of amputation. Failure was due to distal soft tissue injury and venous damage.

was preferred when feasible. Specific lesions will be discussed briefly. In the main, aside from popliteal artery injury, treatment and results do not differ significantly from the vascular registry data (Table 4).

Carotid Arterys Thirty-one patients had carotid artery injuries (Table 5). Twenty-one injuries involved the common carotid and ten the internal carotid artery. Injuries to the external carotid vessel were not included in this study.

Twenty-five patients underwent arterial repair. Nineteen of these patients were neurologically intact preoperatively and remained so postoperatively. Six of the patients undergoing repair were neurologically impaired preoperatively. Following repair, five of those six patients worsened or died and one remained unchanged.

Six patients were treated only by ligation. The two who were neurologically intact before operation remained so after surgical treatment. Four with serious neurologic impairment died.

Aortic Injury: This included one rapid through and through distal aortic arch injury repair with the aorta cross clamped. The two abdominal aortic injuries were similar to a leaking aortic aneurysm with a large retroperitoneal hematoma. Early proximal control facilitated subsequent repair. All three patients survived.

Axillary Artery: This surprisingly frequent injury proved uniformly repairable. The majority were repaired by primary anastomosis.

Brachial Artery: Injury occurred in 75 patients (Table I) in the overall series. Table 6 summarizes the data in American servicemen. Nearly half required vein graft for repair. Furthermore, eight patients with primary end-to-end anastomosis required re-exploration and vein graft interposition. There were four failures, two of which required amputation. Both of these patients had fractures of the humerus and in one, the anastomosis was impaled postoperatively by an unstable fracture fragment. This was the only instance in which an unstabilized fracture clearly contributed to repair failure. The incidence of failure is higher in all extremity vascular injuries with major long bone fracture (Table 7). However, major distal soft tissue injury as a nearly uniform accompaniment of fractures and the actual role of the fracture is difficult to assess.

Iliac Artery Injuries: These are uncommon and nearly always repairable. In all probability, massive iliac

TABLE 2. *24th Evac Hospital 1 July 67–12 August 69* (American Servicemen)

Vessel	Cases	Vein Grafts	Post-op Pulse	Amputation	Failure (Amputation, Ligation or Loss of Pulse)
Carotid	25				
Common	16	4	14		0
Internal	9	0	5		4
Aorta (Includes Subclavian)	3	0	3		0
Axillary (Includes Subclavian)	14	3	14		0
Brachial	64	31	61	2	3
Common Iliac	3	0	3		0
External Iliac	6	2	6		0
Common Femoral	3	2	2		1
Superficial Femoral	65	33	54	9	11
Popliteal	49	27	29	6	12
Totals	232	102	191	17	31

artery injury probably precludes survival sufficient to reach the hospital, accounting for the relative rarity of these injuries.

Femoral Artery: Common femoral injury presented no unusual problems. Amputation rate with superficial femoral injury remains at nearly 12%. Massive soft tissue injury, associated fracture, and venous injury were all associated with an increased failure rate. Sepsis in large soft tissue defects was the common cause of failure beyond a day or so. When soft tissue injury was extensive, every effort was made to repair venous injury as well as arterial injury if present. It frequently seemed that inadequate venous outflow for a leg was a cause of edema with resultant compromise of arteriolar and capillary blood flow and distal ischemia. Two patients had arterial anastomoses at the time of amputation. Venous repair was not always feasible in the femoral area and the importance was not as clearly identified as with popliteal vascular injuries to be discussed next.

Popliteal Injury: Injury to the popliteal artery was the one area in which significant differences existed between the results in the current series and that previously reported. In the overall series, 59 patients underwent popliteal artery repair. There were 13 failures but only seven (11.9%) required amputation (Table 8). Popliteal injuries are evaluated in greater detail because of these improved results. Venous injury and fracture again portended a worse result (Table 9). Every effort was made to repair both the vein and the artery in patients with this particular injury at this hospital. As can be seen, of 29 patients with concomitant venous injury, the vein was repaired in 19 (66%). Furthermore, the success rate of 79% in patients with venous repair compares strikingly with the 30% success rate when the venous injury could not be repaired. Finally, of patients requiring amputation, four had patent arterial repairs at the time. All four had associated venous injury and distal soft tissue defects.

TABLE 3. *Additional Vascular Repairs 24th Evac Hospital* (Not American Servicemen)

Vessel	Cases	Vein Graft	Pulse	Amp	Failure
Carotid	6				
Common	5	1	4		2
Internal	1				1
Axillary	3	1	3		
Brachial	11	4	10		1
Common Fem.	2		2		
Sup. Fem.	12	6	12		
Popliteal	10	2	7	1	1
Totals	44	14	38	1	5

Again, fractures were associated with a much higher failure rate and amputation rate. Patients with fractures usually had significantly greater associated soft tissue injury and loss of venous collateral. It was this phenomenon, rather than fracture instability that appeared to raise the failure rate in this group of patients. In no instance was a failure of superficial femoral or popliteal artery repair the direct result of facture instability in the present series. Overall results of popliteal artery injuries are reported in Table 10.

Discussion

The present report outlines the results of treatment of arterial injuries at one evacuation hospital in Vietnam over an 18-month period. Methods of repair were based on standard principles and technics of vascular repair. Adequate but limited vascular debridement was undertaken in the vast majority of instances for low velocity missile injuries. End-to-end anastomosis was preferred if it could be done without tension. Careful, adequate wound debridement and hemostasis were essential to the prevention of sepsis, a major cause of failure following repair. Fractures may not be internally immobilized with these open, dirty wounds but it was the distinct impression of the authors that adequate external immobilization was sufficient to assure protection of the suture line in extremity injuries.[3]

Two specific areas deserve special emphasis: carotid artery and popliteal artery injuries.

TABLE 4. *Vascular Repair-Early Results*

Vessel	WW II % Amp	W.R.G.H. Registry			24th Evac		
		Cases	Failures	Amp %	Cases	Failures	Amp %
Axillary	50%	22	10	4.5%	13	0	0
Brachial	26%	103	23	2.9%	64	3	3.1% (2)
Aorta		3	0	0	2	0	0
Iliac		3	1	0	9	0	0
Common Fem.	81%	24	6	8.3%	3	1	0
Sup. Fem.	55%	116	24	10.3%	65	11	13.8% (9)
Popliteal	75%	77	23	37.5%	49	12	12.2% (6)
Totals		349	87	12.7%	205	27	8.3% (17)

TABLE 5. *Thirty-one Carotid Artery Injuries*

	Total Cases	Repaired	Ligated
Common	21	20	1
Internal	10	5	5

25 Patients Repaired:
 19 Patients neurologically intact pre-operatively all normal neurologically post-operatively.
 6 Patients neurologically impaired pre-operatively.
  3 died
  2 worsened
  1 no improvement
6 Patients Ligated:
 2 Neurologically intact pre-operatively remained so post-operatively-ligation because technically unrepairable.
 4 Neurologically impaired pre-operatively died.

TABLE 6. *Extremity Vascular Injuries*
(American Servicemen)

Vessel	Cases	Amp.	Amputation Rate	Viable $\bar{0}$ Pulse	Fx.	Fasciotomy
Brachial	64	2	3.1%	1	20	5
Superficial Femoral	65	9	13.8%	2	23	18
Popliteal	49	6	12.2%	6	17	35
Totals	178	17		9	59	53

The present data corroborate accumulated civilian experience with acute strokes due to carotid occlusion. In the presence of a fixed, established neurologic deficit, carotid repair cannot improve and may worsen the ultimate outcome. When neurologic deficit is not established, the carotid injury can be repaired with virtually 100% rate of success and the salvage of an intact functioning carotid vessel on the injured side.[2]

Popliteal artery injury has long been associated with an exceptionally high amputation rate. During W.W. II when ligation was the accepted treatment, the amputation rate was 85%. The Korean War and the early experience with the war in Vietnam indicate an amputation rate of about 33% with repair of popliteal artery injuries. Evaluation of these injuries has substantiated the high proportion of concomitant venous injuries.

In the present series the extreme effort made to perform concomitant venous repair appears to be responsible for the marked improvement in the results of treatment of popliteal artery injuries reported in the present series. The importance of concomitant venous repair has been suggested by Barcia and others[1] and based on the present study, we would recommend it as an essential part of repair of all popliteal and femoral vascular injuries. Interposition saphenous vein grafts are necessary when primary, end-to-end venous repair cannot be established. At the same time, every effort should be made to preserve all existing venous collaterals and the saphenous vein from the injured leg should be preserved if at all possible. Any necessary vein grafts for arterial or venous repair must be obtained from the opposite leg. In bilateral extremity injuries in which amputation was necessary on one side and arterial repair on the other, a piece of uninjured superficial femoral artery was used successfully in two cases instead of saphenous vein.

The use of a vein graft for venous repair is based on the hypothesis that even though the graft has little hope for long-term patency, function for only a few days will be sufficient to prevent massive edema, allow existing edema to subside and new collaterals to be established. A laboratory model in experimental animals is not available to test this hypothesis but it is felt to be strongly supported by the available clinical evidence.

A major problem in the handling of several of these wounds, particularly in the excavating anterior thigh wound with loss of large segments of the superficial femoral artery is the matter of the exposed graft. If at all possible the graft must be covered with viable tissue, either a rotated skin flap or *viable* muscle. An exposed suture line is prone to become infected and hemorrhage even with autogenous tissue. One should consider primary extra anatomic bypasses in this type

TABLE 7. *Influence of Fracture on Outcome of Vascular Repair in Extremities*
(American Servicemen)

			Amputation						Failure*					
Vessel	Total Cases	Total Fracture	Without Fracture		With Fracture		Total		Without Fracture		With Fracture		Total	
			#	%	#	%	#	%	#	%	#	%	#	%
Brachial	64	20 (Humerus)	0	0	2	10	2	3.1	1	2.3	2	10	3	4.7
Superficial Femoral	65	23 (Femur)	2	4.7	7	30	9	13.8	3	7.1	8	34.8	11	16.9
Popliteal	49	17 (Tibia)	1	3.1	5	29.4	6	12.2	2	6.3	10	58.8	12	24.5
Totals	178	60	3	2.5	14	23.3	17	9.6	6	5.1	20	33.3	26	14.6

* Amputation, Ligation or Loss of Pulse

TABLE 8. *Vascular Repair for Popliteal Vessel Injury*

	Successful Repair	Failed Repair	Totals
Arterial Repair	47	12	59
End to End	25	2	27
Lateral Arteriorrhaphy	3	—	3
Vein Graft	19	10	29
Venous Repair			
End to End	7	2	9
Venorrhaphy	5	2	7
Vein Graft	3	—	3
Ligation	3	7	10
Fasciotomy	29	8	37

of case if adequate coverage of a graft is impossible in its usual anatomical position.

In several instances in which separate incision was made for exploration and repair of the arterial injury, primary wound closure was employed with wide debridement of the entrance and exit wounds with delayed primary closure of these wounds on the 4th and 5th day. If the exploration and repair of the arterial injury was performed through the missile wound itself, the wound of injury was then handled in the usual fashion with careful debridement, coverage of the graft with viable tissue when possible and delayed primary closure.

At the time of exploration of the vascular injury the patency of the distal arterial tree must be assessed and patency assured by the passage of Fogarty catheters. In numerous cases good back bleeding was present, yet with passage of the embolectomy catheters extensive thrombotic material was removed. It is axiomatic that back bleeding is no assurance that the major arterial tree distal to the injury is free of thrombosis.

Concomitant fasciotomy was performed in association with repairs of injured brachial, superficial femoral and popliteal arteries (Table 4). In the popliteal artery series in which soft tissue damage and venous injury cause tremendous distal swelling, fasciotomy was employed early and in most of the cases (35 of 49). In the majority of these fasciotomy was carried out at the time of the reconstructive surgery.

TABLE 9. *Type of Popliteal Vascular Injury*

	Successful Repair	Failed Repair	Totals
Arterial Injury	47	12	
Thrombosis	4	0	4
Laceration or Perforation	17	1	18
Transection	26	11	37
Venous Injury	18	11	29
Associated Long Bone Fracture	8	9	17
Massive Distal Soft Tissue Injury	3	8	11

TABLE 10. *Results of Vascular Repair for Popliteal Vessel Injury*

	Successful Repair	Failed Repair
Normal Pulse, Viable Leg	47 (80%)	
Absent Pulse, Viable Leg		5
Amputation		7 (11.9%)
Normal Pulse Non-Viable Leg		4
Failed Repair		12 (20%)
Sepsis	—	2
Re-exploration	2	8
Deaths Unrelated to Vascular Repair	3	1

Conclusion and Summary

Two hundred seventy-six patients with vascular injury treated at the 24th Evacuation Hospital, Republic of Vietnam are reported with an overall success rate of 86.9% and a 6.5% amputation rate. The following principles are of importance in the management of vascular injuries:

1. Wide exposure with careful debridement of the injured extremity.
2. Adequate mobilization of the ends of the debrided artery to allow approximation without tension where possible.
3. Use of reversed saphenous vein graft obtained from the uninjured leg if primary end-to-end anastomosis could not be achieved.
4. Distal thrombectomy in all cases with the Fogarty catheter regardless of the presence of back bleeding.
5. Regional distal heparinization after clearing the distal arterial tree.
6. Repair of any major venous injury whenever technically possible.
7. Covering all grafts with viable tissue. Consider extraanatomic bypass when it is anticipated that coverage cannot otherwise be accomplished.
8. Adequate immobilization of the injured extremity when the vascular injury is associated with unstable long bone fractures.
9. Immediate or early fasciotomy when venous injury and soft tissue damage can be expected to produce significant edema after arterial repair.

References

1. Barcia, P. J., Nelson, T. G. and Whelan, T. J.: Importance of Venous Occlusion in Arterial Repair Failure: An Experimental Study. Ann. Surg., **175**:223, 1972.
2. Cohen, A., Baldwin, J. N. and Grant, R. N.: Problems in the Management of Battlefield Vascular Injuries. Am. J. Surg., **118**:526, 1969.
3. McNamara, J. J., Brief, D. K., Stremple, J. F. and Wright, J. K.: Management of Fractures with Associated Injury in Combat Casualties. J. Trauma (in press).
4. Rich, N. M., Baugh, J. H. and Hughes, C. W.: Acute Arterial Injuries in Vietnam: 1,000 Cases. J. Trauma, **10**:359, 1970.

Muscular Tumors of the Stomach:

Clinical and Pathological Study of 113 Cases

KEVIN MORRISSEY, M.D., EUN SOOK CHO, M.D., GEORGE F. GRAY, JR., M.D.,
BJORN THORBJARNARSON, M.D.

From the Departments of Surgery and Pathology
The New York Hospital-Cornell Medical Center,
New York City

DIAGNOSIS OF most gastric muscular tumors presents little difficulty to the surgeon or pathologist. The commonest type are benign leiomyomas, which are often small lesions found incidentally at operation or autopsy. Leiomyosarcomas are much rarer and their fully malignant nature is usually evident when the lesion begins to cause symptoms. Nevertheless, some benign tumors can also cause symptoms, and, when the histologic appearance is atypical, diagnosis can be difficult. In order to evaluate criteria for benignancy and malignancy, we have studied the clinical histories and pathologic findings of 113 gastric muscular tumors seen at The New York Hospital-Cornell Medical center between 1948 and 1970.

Eighty-three of the patients had leiomyomas, including four with multiple tumors, four had muscular hamartomas, one had hamartoma and leiomyoma, ten had leiomyoblastomas and 15 had leiomyosarcomas (Table 1). There were no rhabdomyomas or rhabdomyosarcomas.

Leiomyomas

Leiomyomas comprised the largest group of gastric muscular tumors. A total of 92 tumors in 83 patients were studied, since one patient with a symptomatic hamartoma had an incidental leiomyoma, two patients had two leiomyomas each and three patients had three tumors each. Twenty-three tumors had an atypical histologic appearance characterized by nuclear prominence with or without marked pleomorphism and without the epithelioid appearance of leiomyoblastoma. We have designated these as "cellular" leiomyomas and the remaining tumors as "ordinary" leiomyomas. Because the cellular leiomyomas may cause more histopathologic difficulty they will be considered separately.

Ordinary Leiomyomas

Ordinary myomas occur in equal frequency in men and women. Slightly over half occur between ages 50–70 and most of the others over age 70. Most of the 60 patients with these tumors were asymptomatic; the lesions were discovered at autopsy in 22 patients and at operation for some other condition in 28. Only 10 patients had symptoms which could be attributed to leiomyoma and resulted in treatment directed primarily to that condition. Pain was the most frequent complaint. Symptoms of gross bleeding or of a mass were uncommon. The symptoms are summarized in Table 2. All of the symptomatic patients had a radiographic filling defect, diagnosed specifically as a leiomyoma in half the cases. No consistent clinical history, laboratory values or radiographic abnormalities could be found in the patients with tumors discovered at autopsy or incidental to other operations. Not surprisingly a large number of these patients had coincidental peptic ulcers, gastric adenocarcinoma or gallbladder disease which was the primary reason for operation.

Grossly, leiomyomas presented as well circumscribed, pale, nodular intramural masses. Smaller tumors were generally confined to the *muscularis propria*, but as size increased, there was distortion of serosa and mucosa. Larger tumors sometimes had a "dumb-bell" shape, prob-

---

Submitted for publication August 25, 1972.

Reprints: Dr. Bjorn Thorbjarnarson, 525 East 68th Street, New York, New York 10021.

TABLE 1. *Mode of Diagnosis of 113 Patients with Gastric Muscular Tumors*

Lesion	Incidental Autopsy	Incidental Operation	Symptomatic Operation
Hamartoma	1	2	2
Ordinary Leiomyoma	22	28	10
Cellular Leiomyoma	3	8	12
Leiomyoblastoma	1	1	8
Leiomyosarcoma	0	1	14
Totals	27	40	46

ably due to less resistance to growth offered by the mucosa and serosa. In most instances, the mucosa was stretched over the tumor and remained intact (Fig. 1). However, in a few cases, ulceration occurred over the mass with a crater extending deep into the tumor. Central necrosis was also seen occasionally.

The size of ordinary leiomyomas was 0.5 to 25 cm, but only seven tumors were larger than 3 cm. and the median size was only 1 cm. The ten tumors in symptomatic patients were all at least 1 cm. in diameter with a median size of 2 cm. (Table 3). Most of the leiomyomas were located on the anterior gastric wall but were rather evenly distributed between fundus, body and antrum. A disproportionate number of the larger tumors of all types were in the fundus and antrum rather than the body of the stomach.

Microscopically, the tumors consisted of bundles of smooth muscle that closely resembled normal muscle so that in many instances only the whorling pattern (Fig. 2) distinguished the tumor from normal musculature. Nuceli tended to be uniform and appeared oval or spindly when seen in longitudinal sections. Multinucleate cells were occasionally seen but mitotic figures were an extreme rarity. In some tumors the nuclei lay in parallel rows, "palisading", a well recognized phenomenon in smooth muscle tumors that should not lead to a diagnosis of a neurogenic tumor even though the appearance is similar to that of the Antoni A areas of neurilemmoma (Fig. 3).

Local excision was adequate therapy. The amount of stomach removed depended on location and size of the tumor. In some instances only an excisional biopsy was needed but an extensive resection was required for a large tumor. No patients died of leiomyoma and no recurrences were recorded.

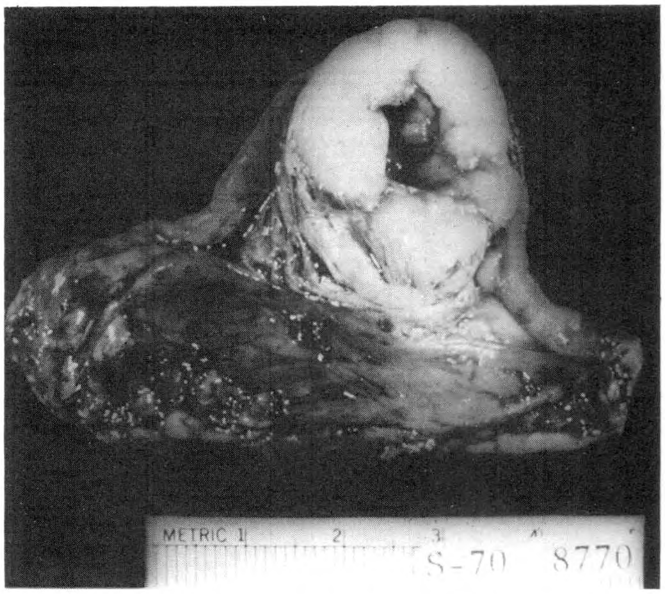


FIG. 1. *Gastric Leiomyoma.* A pale nodular intramural mass protrudes into lumen with stretching of the intact overlying mucosa. Although there is a small focus of central necrosis, the histologic classification was ordinary leiomyoma.

Cellular Leiomyoma

Patients with this histological variant of leiomyoma had the same age and sex distribution as those with ordinary leiomyomas. A smaller proportion, 11 of 23, were asymptomatic, three being incidental findings at autopsy and eight at operation for another condition. The clinical presentation of the 12 symptomatic cases was in general similar to symptomatic patients with ordinary leiomyomas (Table 2), but with a larger number having evidence of gross bleeding. In all of the symptomatic patients a lesion was demonstrated radiographically, but a specific diagnosis of leiomyoma was made only in approximately half the cases.

Although the size range of cellular leiomyomas was similar to ordinary leiomyomas, the median size was larger, 4 cm. and the median size of the tumors causing symptoms was 6 cm. (Table 3). These tumors were somewhat more frequently located on the anterior gastric wall and also more frequently found in the fundus

TABLE 2. *Symptoms in 46 Patients with Muscular Tumors*

No. Pts.	Lesion	Pain	Melena	Hematemesis	Weakness	Weight Loss	Mass	Tenderness
2	Hamartoma	2	1	0	1	0	0	0
10	Ordinary Leiomyoma	5	1	0	0	2	2	2
12	Cellular Leiomyoma	6	7	2	5	2	1	0
8	Leiomyoblastoma	3	3	3	3	2	2	1
14	Leiomyosarcoma	7	5	2	10	6	5	5

TABLE 3. *Size Range (Maximum Diameter in cm.) of Gastric Muscular Tumors*

	All Cases		Incidental		Symptomatic	
Leison	Range	Median	Range	Median	Range	Median
Hamartoma	0.5–2	1.5	*	*	*	*
Ordinary Leiomyoma	0.5–25	1	0.5–6	1	1–25	2
Cellular Leiomyoma	1–20	4	2–11	3	2–20	6
Leiomyoblastoma	1.5–30	5	*	*	1.5–30	5
Leiomyosarcoma	2–25	10	*	*	2–25	10

* Less than three cases.

or antrum than in the body of the stomach. The gross appearance of this group of tumors was similar to that observed in ordinary leiomyomas, namely, an intramural mass, usually firm and paler than the surrounding muscularis. Mucosal ulceration was noted in a third of the cases, probably a reflection of the larger size of these tumors.

Histologically, these lesions were similar to the ordinary leiomyoma except that, in at least some foci, the nuclear:cytoplasmic ratio was increased, giving a cellular appearance (Fig. 4). In some instances giant nuclei or bizarre forms were also observed. Palisading was also frequent. Mitotic figures seemed uncommon, and to confirm this we counted the mitotic figures in 15 high power fields (HPF 500X) in each of the cellular leiomyomas, leiomyoblastomas and leiomyosarcomas. In the cellular leiomyomas there were 0 to 25 mitoses per 25 HPF, the median being two per 25 HPF. The largest number of mitoses seen in any single HPF was four and no mitotic figures were seen in the majority of HPF.

Treatment was local excision, either a wedge resection or partial gastrectomy, depending on the size and location of the lesion. Local recurrence was found at autopsy in one patient who died of an unrelated condition 5 years after diagnosis and local resection, but none of the other patients was known to have any recurrence and none died of tumor.

Hamartoma (Synonyms: Adenomyoma, Heterotopic Pancreas)

These malformations are similar to leiomyomas in clinical presentation and gross appearance. All lesions were small, between 0.5 and 2.5 cm., and were intramural masses in which the most prominent component

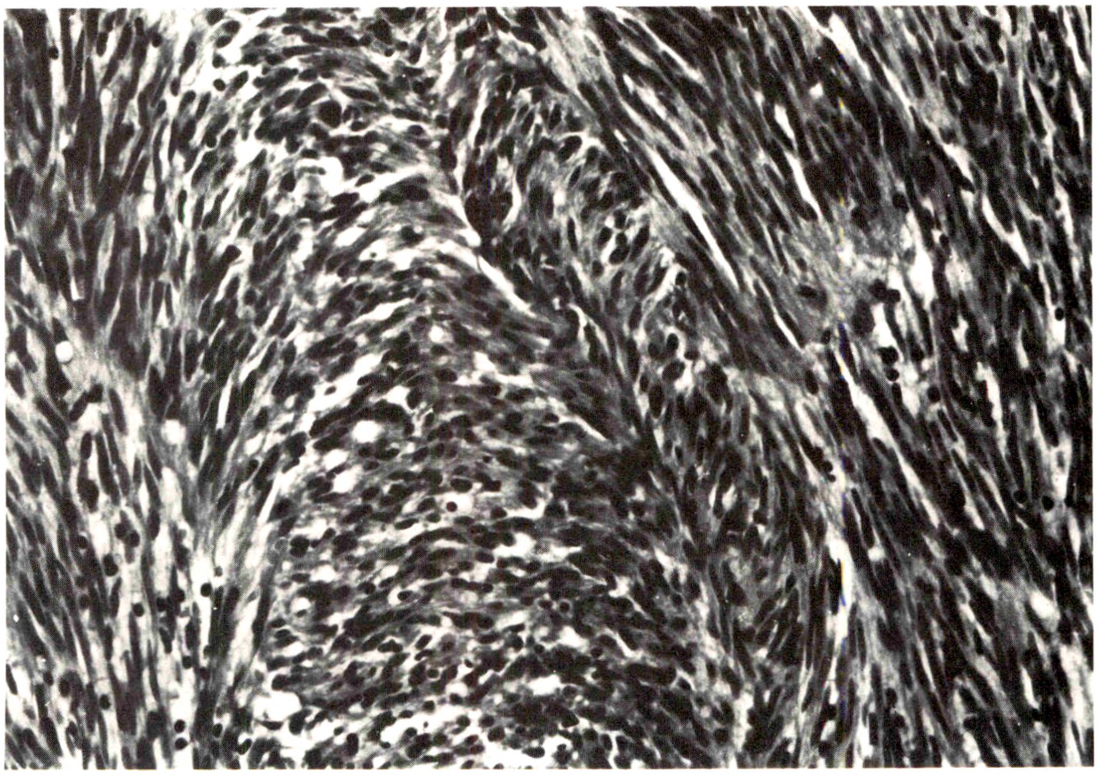


FIG. 2. Whorling pattern of smooth muscle tumors. The spindly cells closely resembling normal smooth muscle lie in interlacing bundles so that some are seen in longitudinal section and others in cross section (H&E 250×).

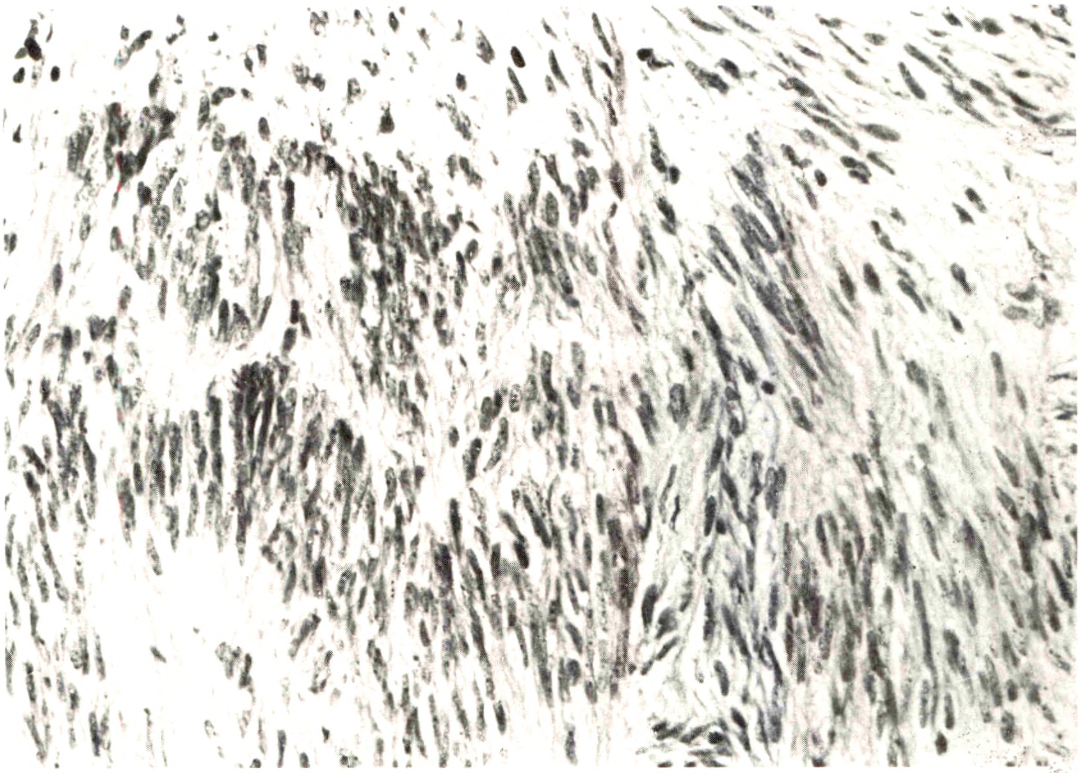


FIG. 3. *Palisading in Leiomyoma.* The elongated, spindly nuclei tend to lie in parallel bundles. This is a common appearance of smooth muscle tumors and does not connote neural origin (H&E 250×).

was interlacing bundles of smooth muscle like that seen in ordinary leiomyomas. However, in each instance, epithelial elements similar to pancreatic or biliary ducts were seen within the muscular bundles. No pancreatic acinar tissue was identified in this group. Three of the tumors were incidental findings at operation or autopsy; two caused symptoms. The age distribution, symptoms, signs and mode of diagnosis were virtually identical

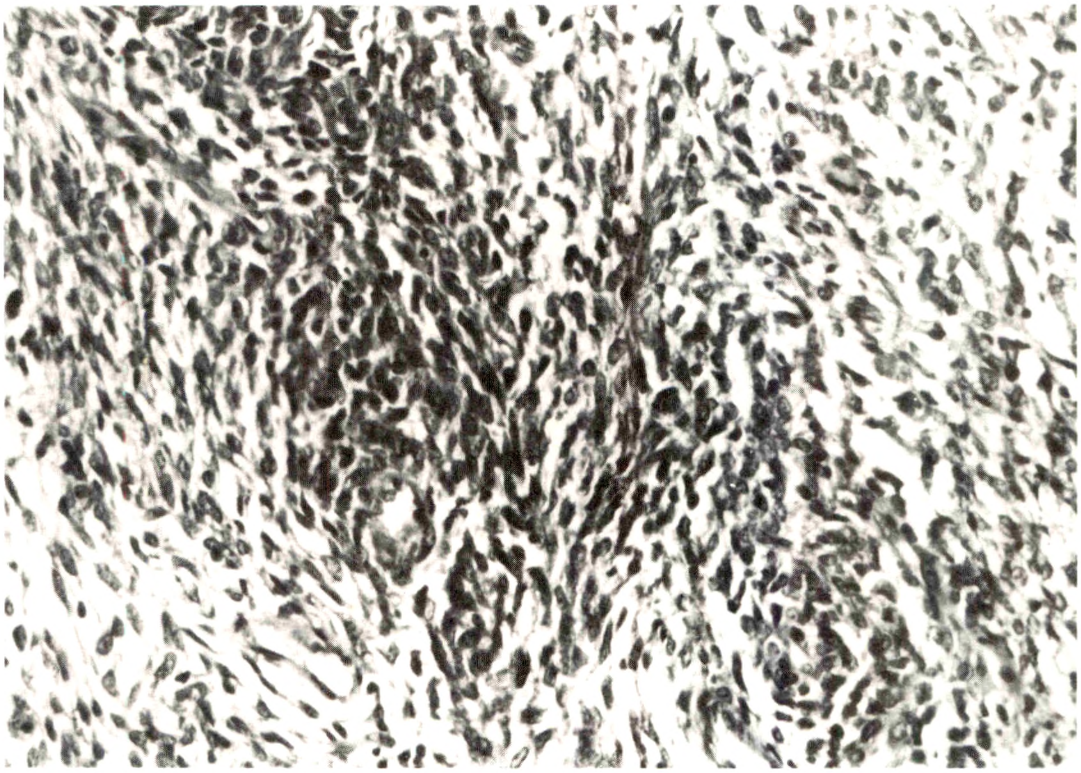


FIG. 4. *Cellular Leiomyoma.* Nuclei are prominent relative to cytoplasm giving a "cellular" appearance. Pleomorphism is often seen focally, but mitoses are rare (H&E 250×).

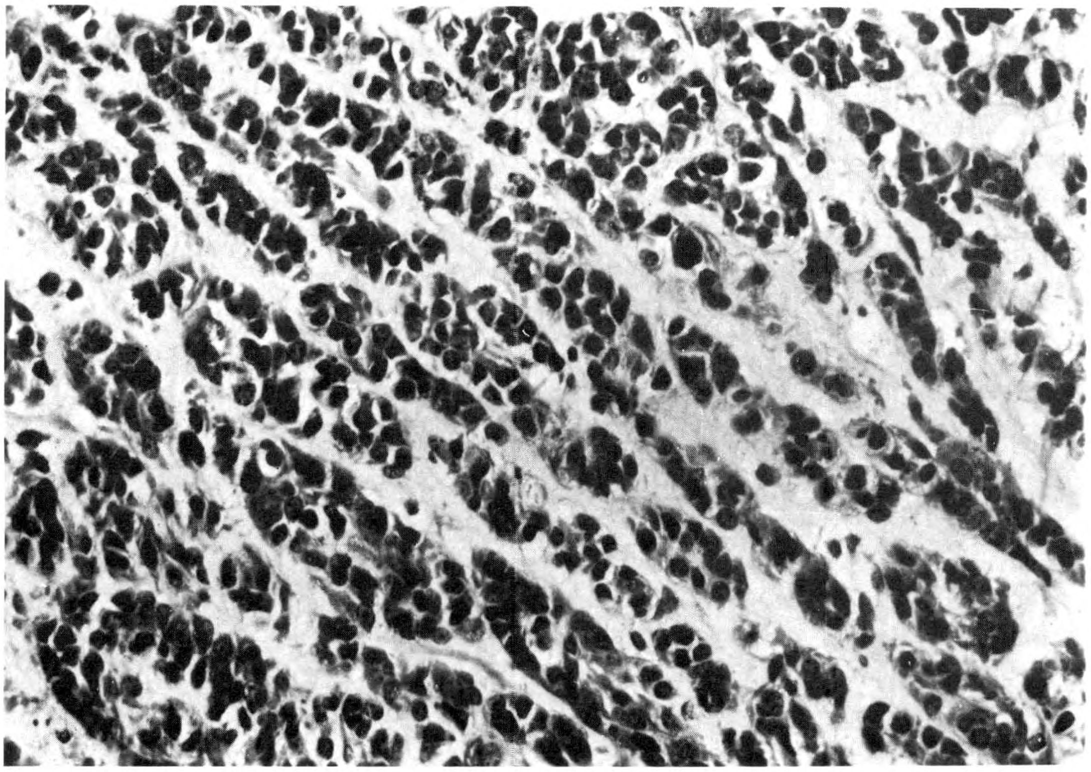


FIG. 5. *Leiomyoblastoma.* In this section the cells are cuboidal and form cords, mimicking carcinoma. Nuclear pleomorphism is seen and some of the cells have clear perinuclear "halos". This is one of several patterns typical of this tumor (H&E 250×). This tumor was 30 cm. in diameter, removed from a 70-year-old man with massive hematemesis. The original classification in 1949 was leiomyosarcoma, but by our present criteria it is a leiomyoblastoma. The patient died 10 years later of unrelated disease with no evidence of recurrence.

to ordinary leiomyomas of similar sizes. Histologic diagnosis depends on identification of ductal or glandular tissue within the smooth muscular mass. Local excision was curative.

Leiomyoblastoma

Ten tumors were classified as leiomyoblastoma, a designation proposed by Stout[4] for a group of relatively uncommon gastric muscular tumors characterized by bizarre histologic appearance, especially round or cuboidal cells with a clear cytoplasm and epithelioid (Fig. 5) or vascular pattern. The term leiomyoblastoma was proposed since it "carried no definite implications or benignancy or malignancy". Actually, only two of Stout's original 69 patients had an unfavorable outcome. Although the pattern said to be typical of leiomyoblastoma was seen in some fully malignant tumors, we have classified all such lesions as leiomyosarcoma and have reserved the designation leiomyoblastoma for those cellular lesions with an epithelioid appearance in which we found no evidence to warrant a diagnosis of sarcoma, in particular no increase in mitoses. We think these are only histologic, not biological variants of leiomyoma, a concept supported by demonstration of smooth muscle elements by electron microscopy,[2] but have retained this classification because it is a recognizable variant of a benign tumor that has been misdiagnosed as leiomyosarcoma, carcinoma or as a vascular or neural tumor.

The clinical presentation of leiomyoblastomas was similar to other cellular myomas with respect to age, symptoms and radiographic findings. The size of leiomyoblastomas range from 1.5 to 30 cm., with a median size of 5 cm. Grossly these lesions resembled other large myomas. Histologically, there was an abundance of cuboidal cells, with clear cytoplasm growing in sheets, strands or clumps, Some foci thus resembled the pattern of anaplastic carcinoma. Some cells also bore a striking resemblance to ganglion cells. The marked vascularity seen in some areas gave the tumor an appearance resembling angiosarcoma or a glomus tumor. The mitotic counts ranged from 0 to 19 mitoses per 25 HPF, with a median of two mitoses per 25 HPF, counts similar to those reported by Stout[4] who found 0 to 19 mitoses in 50 HPF (200X) of 69 leiomyoblastomas.

Treatment of these tumors was the same as for leiomyomas of similar location and size. No recurrences or deaths due to leiomyoblastoma were recorded. This experience is similar to that reported by other authors.[4,5]

Leiomyosarcoma

Patients with malignant tumors had the same age and sex distribution as those with benign tumors. There were eight males and seven females. The tumors most frequently appeared in the sixth and seventh decades, but one patient with a sarcoma was age 14, the youngest patient in the study.

Fourteen of the 15 patients had symptoms. The remaining patient had a 2 cm. intramural gastric lesion, which we interpreted as leiomyosarcoma, that was found incidental to esophageal resection for epidermoid carcinoma. The symptoms in this instance were attributed to the carcinoma. In the 14 symptomatic patients, pain was the most frequent complaint. Several patients also had bleeding, weight loss, weakness or a mass (Table 2). A radiographic lesion was demonstrated in 13 of the 14 symptomatic patients.

Leiomyosarcomas were larger than the benign tumors, the range being 2 to 25 cm., with a median of 10 cm. (Table 3). Because of the larger size, intramural origin was less apparent and ulceration of the mucosa was more frequently observed (Fig. 7). Also hemorrhage and focal necrosis was present in many instances. Four tumors had grossly apparent extension to other organs or metastases at the time of diagnosis (Fig. 8). Invasion of adjacent organs such as liver or spleen and peritoneal dissemination were the most common types of spread. Metastases beyond the abdomen were demonstrated histologically in only two instances.

Microscopically, considerable variation was seen in the sarcomas. In some instances, the tumor focally resembled ordinary leiomyoma with whorling masses of spindly cells with fairly abundant cytoplasms. However, in most tumors there was a cellular appearance and some nuclear pleomorphism with giant and bizarre forms was observed in all instances. In a few cases, bizarre cellular changes were present only in a few foci, emphasizing the necessity for adequate tissue sampling in large muscular tumors. There were 25 to 305 mitoses per HPF with a median of 41 mitoses per 25 HPF (Fig. 8). Thus, on average at least one mitotic figure per HPF was found in each sarcoma. Each sarcoma also had at least one HPF with four mitoses and most of the sarcomas had several fields with six or more mitoses. The largest number of mitoses counted in any one HPF was 21, but more than ten mitoses per HPF was very uncommon. In contrast, the largest number of mitoses seen in any HPF of a benign tumor was four and the majority of fields in the benign tumors had no mitotic figures.

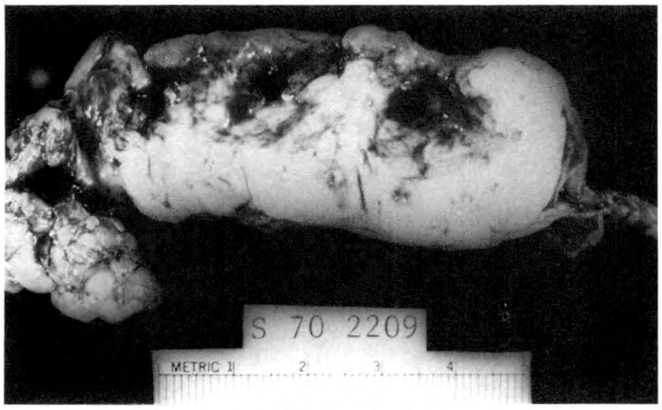


FIG. 6. *Gastric Leiomyosarcoma.* This large intramural tumor protrudes into the lumen. The overlying mucosa is ulcerated with the crater extending deep into the lesion. A small gastroscopic biopsy was interpreted as cellular leiomyoma since mitoses were not seen. In the resected tumor numerous mitotic figures were found and the correct diagnosis of leiomyosarcoma was established. The patient had peritoneal dissemination 2 years after subtotal gastric resection.

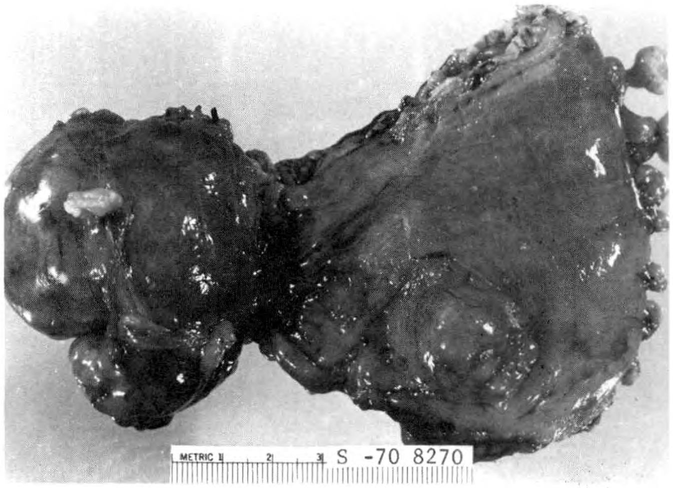


FIG. 7. Primary gastric leiomyosarcoma with mesenteric metastasis. The primary tumor bulges from the serosa, lower right, and also formed an ulcerating intraluminal mass. At left is a huge metastasis within the omentum. The patient was a 45-year-old man who developed sudden massive bleeding, a clinical feature of many large gastric muscular tumors. There has been no evidence of recurrence 2 years after partial gastric resection.

The treatment of the 14 patients with leiomyosarcoma diagnosed preoperatively consisted of either a partial or total gastric resection. One of these patients died postoperatively in the hospital. Two were lost to follow-up and presumed dead of the disease. Eight patients died of sarcoma between 7 and 30 months after surgery with a median survival time of 16.5 months. One patient was alive with known recurrence 24 months after operation. Another patient died of heart disease one year after operation clinically free of tumor. Finally, one patient was still alive and well 2 years after operation. The results are thus very discouraging, reflecting invasion or metastases already evident at the time of operation.

Changes in Diagnosis

All of the pathologic material was received without knowledge of the previous diagnosis or clinical follow-up; we then found on the basis of our histologic study, including evaluation of mitotic activity, that we had classified as cellular leiomyoma or leiomyoblastoma eight cases previously diagnosed as leiomyosarcoma. Some of

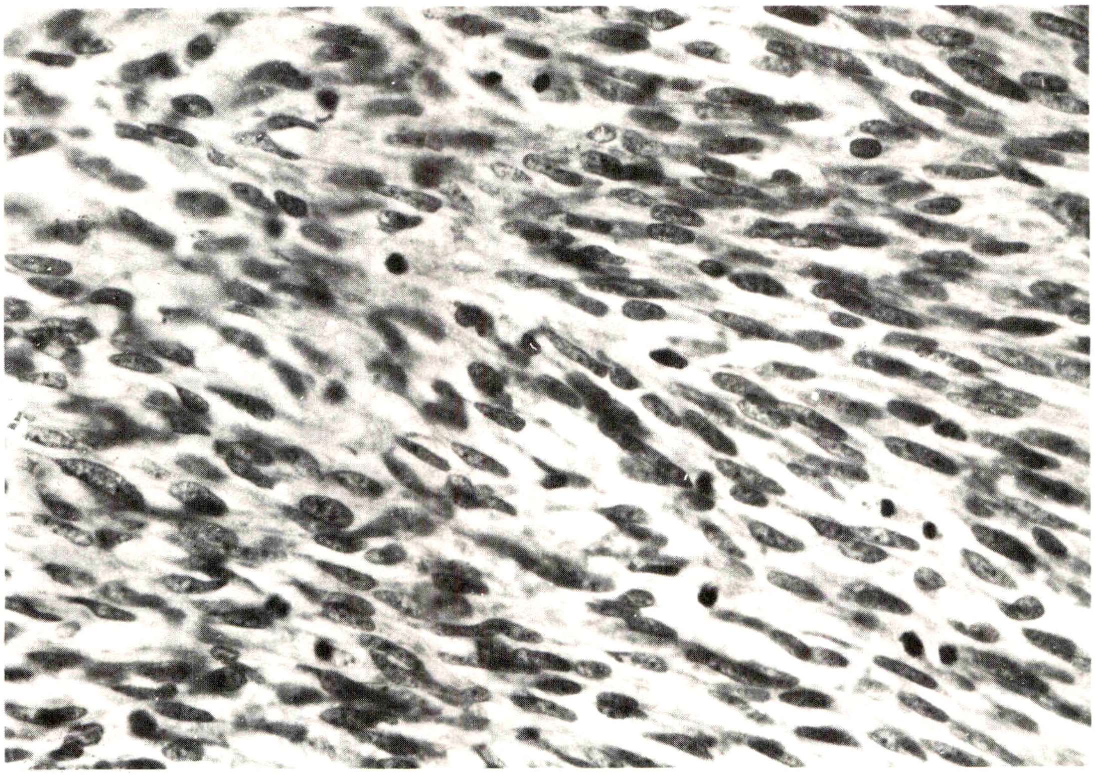


FIG. 8. *Leiomyosarcoma.* Most of the cells closely resemble leiomyoma, but numerous mitotic figures are apparent in this field. The lesion proved fatal (H&E 400×).

these were first diagnosed as sarcoma before Stout's[4] description of leiomyoblastoma in 1962. We also had classified one tumor as sarcoma which had previously been diagnosed as leiomyoma. None of the eight patients with revised diagnosis of a benign tumor had died of disease and none had known recurrence up to 96 months after therapy. The patient with a revised diagnosis of sarcoma was the one with the tumor found incidentally during treatment of an ultimately fatal esophageal carcinoma. The only other change in diagnosis was one instance of reclassification of a small lesion, previously called leiomyoma, as a hamartoma after examination of deeper cuts of the original paraffin blocks revealed ductal elements. Such a distinction is obviously of no clinical importance.

While we recognize the possibility of overlooking evidence of malignancy in an otherwise benign appearing large muscular tumor, our findings point to the need of recognition that certain patterns of bizarre muscular tumors are associated with a favorable clinical course and that erroneous classification of cellular leiomyomas or leiomyoblastomas as leiomyosarcoma can easily occur unless careful study of mitotic activity is done.

Discussion

Although the majority of gastric muscular tumors are discovered incidental to operation for another condition or at autopsy, approximately 40% of the lesions we studied had caused symptoms which led to surgical treatment. Of the tumors causing symptoms, the benign lesions, including leiomyomas, leiomyoblastomas and hamartomas were approximately twice as numerous as the leiomyosarcomas.

In many instances the correct diagnosis of these large gastric muscular tumors was difficult and we found no difference in the clinical presentation of benign and malignant tumors with respect to sex, age or symptoms. Virtually all symptomatic patients had a radiographic filling defect, but exact classification by X-ray studies was possible in less than half the cases. Exfoliative cytology and gastroscopic inspection were also of little value in making a definite diagnosis. Furthermore, while it is true that nearly all sarcomas were large, benign tumors also attained enormous size. Indeed, three of the five largest tumors in this study were benign, including the largest lesion, a 30 cm. in diameter leiomyoblastoma. Microscopically, palisading of nuclei, a cellular appearance, and pleomorphism were found in benign lesions as well as sarcomas. In the absence of gross extension or metastases, the most reliable index for diagnosis of leiomyosarcoma was demonstration of increased mitotic activity which was found, at least focally, in all sarcomas. An average mitotic rate of more than one per HPF was a consistent feature of gastric leiomysarcomas. A similar criterion has also been of value in diagnosis of smooth muscle tumors of intestine[3] and uterus.[1]

A large gastric tumor must be thoroughly studied microscopically, since the greater part of some sarcomas will have a benign appearance. Because of this, the limitations of frozen section diagnosis must be appreciated by pathologist and surgeon alike. In many instances the frozen section will be most useful in determining that a lesion is a muscular tumor and not carcinoma or lymphoma, the final diagnosis depending on study of many paraffin sections.

Summary

Forty-six of 113 patients with primary gastric muscular tumors had symptoms which led to diagnosis and treatment of the lesion. Among the remaining patients the tumors were incidental findings at abdominal surgery or at autopsy. The clinical presentation and gross appearance provided no reliable means for accurate differential of benign and malignant lesions. The diagnosis of malignancy can be established only by thorough histologic study with demonstration of increased mitotic rate since many large, ulcerating gastric muscular tumors with bizarre histologic features are benign.

References

1. Novak, E. R. and Woodruff, J. D.: Gynecologic and Obstetrical Pathology, Philadelphia, W. B. Saunders, 1967, p. 241.
2. Salazar, H. and Totten, R. S.: Leiomyoblastoma of the Stomach, An Ultrastructural Study. Cancer, **25**:176, 1969.
3. Starr, G. F. and Dockerty, M. B.: Leiomyomas and Leiomyosarcomas of the Small Intestine. Cancer, **8**:101, 1955.
4. Stout, A. P.: Bizarre Smooth Muscle Tumors of the Stomach. Cancer, **15**:400, 1962.
5. Tallquist, G., Salleda, H. and Lindstrom, B. L.: Leiomyoblastoma of the Stomach: A Clinicopathological Study of Ten Cases. Acta. Pathol. Microbiol. Scand., **71**:194, 1967.

Hepatic Arterial Patency and Complications after Catheterization for Infusion Chemotherapy

BLAKE CADY, M.D.

From the Department of Surgery, Lahey Clinic Foundation
Boston, Massachusetts

THE CONCEPT of the regional arterial infusion chemotherapy for hepatic malignancy is well established. Numerous technics have been reported in the literature and Watkins *et al.*[9] have defined a standardized technic utilized at the Lahey Clinic Foundation. No publication has reported the actual fate of the infusion catheter or the hepatic artery, and this information is essential in evaluating the importance of operative placement of such catheters. In addition, a recent report[3] indicated a significant incidence of gastrointestinal hemorrhage after intra-arterial chemotherapy of hepatic malignancies and occasional arterial thrombosis and needs substantiation.

Material and Methods

Eighty-one consecutive primary operative hepatic arterial catheterizations with a standard Teflon catheter* performed for malignancy before 1971 were chosen because criteria of patient selection were reasonably uniform, surgical technics had been standardized, and follow-up procedures were detailed. These surgical procedures sometimes included resection of a primary colon cancer or dilatation or intubation of an obstructing bile duct carcinoma. The technics of operative compensation for anatomic arterial variations have been described by Watkins and associates.[9]

Preoperative selective celiac and superior mesenteric artery angiography was considered essential because of the known anatomic variations and was performed by way of the femoral artery with the usual Seldinger guide wire technic in all but two patients. Postoperatively, catheter angiograms were obtained by attaching the Teflon catheter to a pressure injector set at 800 pounds per square inch, which achieved a flow of roughly 2 cubic centimeters per second of one of the common angiographic dyes. This flow was sufficient in nearly all cases to produce radiographic opacification of the catheterized artery and a subsequent capillary phase hepatogram for evaluation of catheter and hepatic arterial patency, catheter tip migration, and hepatic response in terms of size of the liver and the metastatic nodules.

Such catheter arteriography was performed before the patient was discharged from hospital following surgical catheter placement, generally about 1 week after operation and subsequently at 6-week to 10-week intervals for about 6 months. After this, catheter angiography was performed less regularly. Any drug administration by way of the catheter that caused pain, or any deterioration of the clinical situation, warranted repeated angiography. If confusion about the state of the hepatic arterial patency persisted after catheter angiography, repeated percutaneous selective celiac and superior mesenteric artery angiography was performed.

Treatment with chemotherapeutic agents by way of the hepatic arterial catheters was continued, except during episodes of hepatic toxicity, for as long as vessel patency could be documented. A few patients had continued catheter infusion of drug after hepatic arterial thrombosis was demonstrated when dye flow at angiography was seen to proceed by way of splenic artery, splenic vein, and portal vein to liver. However, hepatic arterial thrombosis was acknowledged.

Results

Eighty-one patients with a variety of primary and metastatic hepatic or biliary carcinomas had hepatic arterial catheters placed at a surgical procedure.

Of these patients, 79 had preoperative selective arterio-

Submitted for publication May 31, 1972.

* United States Catheter and Instrument Corporation, Glens Falls, New York.

graphic studies. Table 1 demonstrates the arterial anatomy seen. Normal anatomy implies that the common hepatic artery arose from the celiac artery, and no angiographically discernible arterial supply otherwise went to the liver.[4] A right replaced hepatic artery indicated that some or all of the arterial supply to the right lobe arose from the superior mesenteric artery. In two patients, the entire hepatic arterial supply arose as a trunk from the superior mesenteric artery. In seven patients, a gastrohepatic trunk arose from the celiac axis which supplied, after the left gastric branching, a major or minor portion of the left hepatic lobe.

Table 2 demonstrates the type of catheterization performed and the adequacy of hepatic tissue coverage as evidenced by hepatic fluorescence at the time of operation. Complete coverage of hepatic substance by infusion through a single catheter was accomplished in 85% of patients. Operative compensation for anatomic variations was achieved in seven patients (9%). In one such patient, anastomosis between the gastroduodenal artery and the right replaced hepatic artery has remained patent for 3 years. In another, ligation of a minor right replaced hepatic artery achieved crossover fluorescence from the normal major right hepatic artery, and this was documented by catheter angiography. In five instances of left gastrohepatic vessels, coverage was achieved by catheterizing the celiac axis by way of the splenic artery. Two catheters, one in the replaced right hepatic artery and one in the left hepatic artery by way of the gastroduodenal artery, were required to achieve complete hepatic coverage in four patients. Eight patients had only partial hepatic infusion by way of one catheter. Involvement primarily of the right lobe usually dictated this approach. In two patients, subsequent progression of left hepatic metastases caused death while the right lobe disease remained controlled. Currently, all patients receive total hepatic coverage, even if two catheters are required.

Postoperative catheter angiography was performed on 73 patients (Table 3). Three patients died postoperatively, and three had rapidly deteriorating clinical situations. One patient extracted the catheter during postoperative psychosis, and one catheter was removed because no preoperative arteriography had been performed and proper catheter infusion could not be obtained.

TABLE 1. *Hepatic Arterial Catheter Placement*

Vascular Anatomy		
	Number of Cases	Per Cent
"Normal"	58	73
Right replaced hepatic artery, total or partial	12	15
Left gastrohepatic	7	9
Common hepatic entirely from superior mesenteric artery	2	3
	79	100

TABLE 2. *Hepatic Arterial Catheter Placement*

Catheter Function			
		Number of Cases	Per Cent
One catheter: Complete hepatic coverage		67	85
Normal	58		
Left gastrohepatic artery	5		
Right replaced hepatic artery	2		
Common hepatic artery from superior mesenteric artery	2		
One catheter: Partial hepatic coverage		8	10
Right replaced hepatic artery	6		
Left gastrohepatic artery	2		
Two catheters: Complete hepatic coverage		4	5
Right replaced hepatic artery	4		

It is obvious that the last demonstrated proof of patency is considerably less than actual arterial patency, since the interval between catheter angiography was generally 6 to 10 weeks. In many patients, this interval was much longer after the second or third angiogram. If a prolonged interval occurred and the next angiograms showed occlusion, the last normal angiogram was selected as the time of proven patency. Even with these qualifications, the median duration of proven hepatic arterial patency was 12 weeks.

The actual fate of the hepatic artery after operative

TABLE 3. *Time of Hepatic Arterial Patency in Weeks*

			Number
Hepatic arterial catheters placed			81
No postoperative catheter angiogram		8	
Postoperative death	3		
Patient markedly deteriorated	3		
Early catheter removal	2		
Postoperative catheter angiograms			73
Weeks postoperative of last demonstrated hepatic artery patency			
1 to 2	12		
3 to 4	2		
4 to 6	10		
8 to 10	11		
12 to 14	8		
16 to 18	7		
20 to 24	7		
28 to 32	7		
36 to 40	5		
55	1		
64	2		
104	1		

Median patency—12 weeks
Range, 1–104 weeks

TABLE 4. *Fate of Hepatic Artery*

			Number
Proved arterial thromboses by angiography			18
Within 2 weeks			4
Later recanalized and patent	1		
Infusion via splenic artery	2		
2 weeks to 8 weeks		8	
Infusion via splenic artery	2		
8 weeks to 26 weeks		5	
Infusion via splenic artery	1		
Time not known		1	
Proved arterial patency by angiography in patients presently still alive			9
Median survival and patency 13 months (range, 5 to 36 months)			
Presumed arterial patency until death			
Angiograms proved patency for at least 67% of life duration			18
Exact status of hepatic artery unknown			28
Living (19, 24, 30 months) catheter out	3		
Dead, angiogram proved patency for less than 67% of life duration	25		
			73

catheterization is shown in Table 4. Only 18 patients had angiographically proven arterial thrombosis, and five of these had regional therapy then conducted with the same catheter by way of the splenic artery as angiograms showed hepatic infusion by this route (splenic artery to splenic vein to portal vein). Some clear hepatic responses occurred in this way. One other patient subsequently demonstrated recanalization and received therapy. Two patients had slowly progressive thrombosis of the hepatic artery demonstrated angiographically over a period of 4 and 6 months before complete occlusion and received an adequate course of therapy.

Nine patients are still living with proven patency of the hepatic artery for periods from 5 to 36 months. Three of these patients had catheter removals at 6, 22, and 40 weeks because of migration or accident, and all three have had second catheter insertions for recrudescent disease. One is alive at 31 months, and two died at 26 and 38 months.

Catheter patency until death was assumed in 18 patients when the last arteriogram demonstrating patency was more than two thirds through the time period from operation to death. These survival periods ranged from 1 to 26 months.

Twenty-eight patients could not have the actual fate of the hepatic artery catheter evaluated since they died long after their last angiogram or are living but without a current catheter by which to perform angiography.

Therefore, 45 patients have evidence of the actual fate of the hepatic artery for periods ranging from 1 to 36 months. Of those patients, 18 (40%) had known thrombosis, and 27 (60%) were known or presumed to remain patent. Of the 18 known thromboses, 12 (67%) occurred within 8 weeks (Table 4). Of 22 patients with proven or presumed patency, 20 remained patent for more than 5 months. It can thus be seen that most thromboses occur within 2 months and that, if patency persists for 5 months, it usually is permanent.

Taking together the data of Tables 3 and 4, it can be seen that the median proved patency time of 12 weeks is conservative and may indeed be considerably longer. Furthermore, in the presence of thrombosis, 44% of patients were able to be treated regionally as described, and 33% had thrombosis late so that an adequate course of therapy was given.

The characteristics of 18 patients with more than 6 months of proven arterial patency were analyzed (Table 5). Obviously, survival was prolonged, but no other distinctive features were evident when compared to the entire group or to those with less than 1 month of arterial patency.

Three operative deaths occurred; all patients had massive hepatic enlargement, massive ascites, and evidence of significant portal hypertension. No operative deaths have occurred in the past 2 years when evidence of significant portal hypertension or massive ascites has contraindicated operation. Liver size alone is not important. Although several patients with all three features have tolerated operative catheter placement in the past, currently, such patients are subjected to percutaneous catheter placement.

Complications related directly to catheter angiography are shown in Table 6. Although 30% of patients had demonstration of angiographic dye extravasation during

TABLE 5. *Patient Characteristics with Prolonged Arterial Patency*

		Number of Patients	Per Cent
6 Months or more of arterial patency		18	25
Age			
Under 50	3		
50 to 60	10		
Over 60	5		
Primary cancer			
Colon		17	
Other		1	
Anatomy			
Normal		12	
Variation		6	
Drug toxicity			
None		2	
Occasional		11	
Frequent		5	
Evidence of arterial injury			
Dye extravasation angiographically		7	
Catheter migration		1	
Pain with catheter angiogram		6	
Pain with drug infusion		1	

at least one angiogram and many patients had repeated evidence of dye extravasation, there seemed to be no clear relationship to arterial thrombosis. Hepatic arterial thrombosis actually developed in less than one third of these patients; the time and incidence were not dissimilar from the group as a whole.

Ten percent of the patients had actual migration of the catheter outside the artery, usually into the biliary tract. The causes and processes of this migration are obscure but are presumably related to the relative stiffness of the Teflon catheter and its resultant attempts to straighten when a curve is necessary in its course from the gastroduodenal artery upstream into the common hepatic artery. Despite the clear demonstration of the catheter lying within the biliary system by dye injection and the occasional simultaneous demonstration of both artery and bile duct, in no case was the intrabiliary migration a source of morbidity. No bile fistula, hemobilia, biliary obstruction, or hemorrhage was observed. All six catheters were removed promptly on diagnosis, and no complications resulted. Catheters were removed by continuous pull and slight finger pressure at the skin site after extraction to stop the occasional brief, slight, arterial bleeding.

A duodenal fistula developed in one patient, presumably on the basis of pressure erosion by the catheter during the terminal phase of advancing malignancy. This persisted despite catheter extraction and was a significant but not major problem in terminal patient care.

No instance of primary catheter obstruction occurred while infusion continued. Thus, the small bore Teflon catheter with one-way valve preventing catheter tip blood entrance seems to be mechanically extremely satisfactory.

Of 73 patients, 11 had some manifestations of acid-peptic ulceration of the upper gastrointestinal tract after initiation of drug therapy (Table 7). Five patients died as a result of massive bleeding 8, 6, 4, 3, and 2 months after catheter placement; all were over the age of 60. One patient had had an anastomotic ulcer with bleeding following pancreaticoduodenectomy before catheter placement and fatally bled from ulcerative esophagitis.

TABLE 6. *Catheter Complications*

		Number	Per Cent
Extravasation of dye by angiography		24	30
Early hepatic artery occlusion	2		
8-week hepatic artery occlusion	5		
Late hepatic artery occlusion	4		
Migration of catheter		8	10
Into bile ducts	6		
Outside hepatic artery	1		
Combined duodenal and bilary fistula	1		
Catheter occlusion while actively infused		0	

TABLE 7. *Acid-Peptic Disease of Upper Gastrointestinal Tract after Infusion Chemotherapy*

	Number of Patients	Per Cent
All cases with evidence of acid-peptic disease	11	15
Nonfatal hemorrhage	8	11
Multiple episodes of nonfatal hemorrhage	3	
Hemorrhage causing death	5	7
Duodenal ulcer perforation causing death	1	
Actual demonstration of duodenal ulcer by X-ray, postmortem, or surgery	6	

Another patient had had vagotomy and posterior gastroenterostomy for documented duodenal ulcer disease 10 years before hepatic arterial catheterization.

The death from perforated ulcer occurred in a 46-year-old man 1 month after double catheterization for a

TABLE 8. *Patient Characteristics in Acid-Peptic Complication of Infusion Chemotherapy*

		Number
Age		
Under 50		2
50 to 60		4
Over 60		5
Primary cancer		
Colon		7
Other		4
Hepatoma	1	
Breast	1	
Carcinoid	1	
Islet cell pancreas	1	
Anatomy		
Normal		6
Variation		5
Right replaced	3	
Left gastrohepatic	2	
Drug toxicity		
None		2
Occasional		9
Stage of disease		
Asymptomatic		2
Mild symptoms		3
Moderate symptoms		4
Severe symptoms		2
Size of liver		
Not palpable		1
Slightly enlarged		2
Moderately enlarged		4
Massive		4
Degree of liver replacement at surgery		
Less than 25%		1
25 to 50%		6
50 to 75%		4
Liver response to therapy		
Marked improvement		3
Some improvement		4
No change		4
Clinical response to therapy		
No improvement		1
Minor improvement		1
Decreased symptoms		3
Returned toward normal life		3
Resumed normal life		2

25-year history of carcinoid syndrome and massive hepatic carcinoid metastases.

Several nonfatal hemorrhages occurred at times completely disassociated from episodes of infusion chemotherapy and in one case long after catheter removal.

Common characteristics of the 11 patients with acid-peptic ulceration were searched for (Table 8). No universal correlations were noted; however, most patients had moderately advanced to severe symptoms and greatly enlarged livers, and eight of the 11 patients had significant improvement in their clinical situation and hepatic evaluation and function. It is of interest that five patients with hemorrhage over the age of 60 died.

Discussion

The procedure of operative hepatic arterial catheter placement for the treatment of hepatic malignancy by regional infusion chemotherapy has produced suggestive improvements in hepatomas,[1] metastases from colon cancer,[2,9] and islet cell carcinoma of the pancreas.[9] In these conditions, systemic chemotherapy has been shown to be of little or no benefit,[6,7,8]and curative surgical resection is uncommon.

Our results indicate that operative hepatic arterial catheterization can be performed with minimal mortality (3.7%), and with more stringent patient selection, there should be negligible operative mortality. Few serious or fatal complications result from the presence of the catheter or this method of drug administration. Although 11% of patients had evidence of acid-peptic ulceration in the esophagus, stomach, or duodenum, and 8% of all patients died from resulting hemorrhage or perforation, it is unknown what the incidence of these problems is in cancer patients with metastases generally or when treated with systemic chemotherapy or radiation therapy. Certainly, severe physical and psychologic stress, the magnitude of which is unfamiliar to the population as a whole, is common. Most episodes of hemorrhage were not directly related to drug administration; the patients who died from hemorrhage had, without exception, received several previous courses of chemotherapy without incident. Nor were episodes of hemorrhage or perforation associated with episodes of chemical toxicity of the liver or bone marrow.

Arterial branches to the stomach or duodenum may be conducting drug and causing direct mucosal toxicity and erosion; we have rarely encountered this. (One patient from another unit who inadvertently received drug in the left gastric artery demonstrated nausea and repeated vomiting without bleeding.) In the course of catheter placement, we routinely ligate the gastroduodenal artery and usually the right gastric artery and never observe gastric or duodenal fluorescence when this material is used to check catheter position. Drug distribution in the gastrointestinal tract is therefore unlikely. Lucas *et al.*[3] attribute such bleeding to drug effect on gastroduodenal mucosa, frequently in the presence of hepatic arterial occlusion, suggesting aberrent vascular flow patterns. We did not note a particular association with hepatic arterial thrombosis. Thus, neither the operative procedure, the presence of the catheter, nor antimetabolite chemotherapy by way of the catheter directly seems to cause gastrointestinal bleeding. This is a manifestation of acid-peptic disease in patients who are stressed severely and for prolonged periods. Certainly the high incidence of acid-peptic disease should be recognized and preventive measures utilized.

Median hepatic arterial patency of 12 weeks seems adequate for regression by continuous antimetabolite infusion chemotherapy and is considerably less than the presumed total patency duration. Three months of infusion chemotherapy is required to achieve maximum benefit and, therefore, this median patency seems adequate. In only seven patients (10%) did arterial thrombosis prevent regional therapy for at least 8 weeks, and this period seems sufficient to achieve major gains in survival and symptom relief. Many of the short, proven patency intervals were, of course, related to patients who did not respond to chemotherapy and died early without as detailed a followup as responders. However, two of the 15 patients with 4 weeks or less of proven patency lived for periods of 16 and 25 months, and one is still living with stable disease at 19 months.

In no patient was it believed that arterial occlusion caused significant clinical deterioration. Sudden onset of hepatic failure, hepatic necrosis, or jaundice was not observed except when related to chemical toxicity, and no cases of hepatic tissue necrosis were observed at autopsy, although necrosis of tumor nodules was frequently observed. Indeed, it has been reported[5] but not confirmed that hepatic arterial ligation itself can cause regression of hepatic metastases. However, in no patient did the onset of clinical improvement coincide with arterial thrombosis. In nearly all patients, objective regression of disease occurred before thrombosis.

Although 10% of the catheters migrated out of the hepatic artery, only one serious complication resulted and this occurred preterminally. None of the catheter migrations into the biliary tree caused significant symptoms or detectable bleeding and all occurred after a prolonged period of therapy.

Summary

Large numbers of patients die each year from hepatoma, bile duct carcinoma, gallbladder carcinoma, and liver metastases from colon cancer. A beginning has been made in attempts at palliation of these largely unresectable and incurable conditions by the use of regional arterial infusion chemotherapy.

Results of operative placement of hepatic arterial catheters are presented. Nearly all anatomic situations can be accommodated, complications directly related to catheter positioning and location were not serious, and long-term catheter and hepatic arterial patency can be expected in about 90% of patients. Eleven per cent of patients will manifest acid-peptic disease of the upper gastrointestinal tract, and two thirds of these will die from resulting massive hemorrhage. Whether this is related to catheter position or drug infusion seems unlikely. Metastatic cancer patients are certainly severely stressed, both physically and psychologically, and thus should be monitored for a history or current evidence of gastric hypersecretion, duodenal or gastric ulceration, and development of portal hypertension and esophageal varices.

References

1. Cady, B. and Oberfield, R. A.: Arterial Infusion Chemotherapy of Hepatomas (in preparation).
2. Cady, B. and Oberfield, R. A.: Regional Infusion Chemotherapy of Hepatic Metastases from Carcinoma of the Colon. Am. J. Surg. (in press).
3. Lucas, R. J., Tumacder, O. and Wilson, G. S.: Hepatic Artery Occlusion following Hepatic Artery Catheterization. Ann. Surg., 173:238, 1971.
4. Michels, N. A.: Blood Supply and Anatomy of the Upper Abdominal Organs with a Descriptive Atlas. Philadelphia, J. B. Lippincott, 1955, 581 pp.
5. Nilsson, L. A.: Therapeutic Hepatic Artery Ligation in Patients with Secondary Liver Tumors. Rev. Surg., 23:374, 1966.
6. Plengvanit, U. and Viranuvatti, V.: Treatment of Primary Carcinoma of the Liver with Nitrogen Mustard and Prednisolone: Report of 51 Cases. Am. J. Gastroent., 42:521, 1964.
7. Rapoport, A. H. and Burleson, R. L.: Survival of Patients Treated with Systemic Fluorouracil for Hepatic Metastases. Surg. Gynec. Obstet., 130:773, 1970.
8. Vogel, C. L., Adamson, R. H., DeVita, J. T., Johns, D. G. and Kyalwazi, S. K.: Preliminary Clinical Trial of Dichloromethotrexate in Hepatocellular Carcinoma. Cancer Chemother. Rep. (in press).
9. Watkins, E., Jr., Khazei, A. M. and Nahra, K. S.: Surgical Basis for Arterial Infusion Chemotherapy of Disseminated Carcinoma of the Liver. Surg. Gynec. Obstet., 130:581, 1970.

Treatment of Primary and Secondary Liver Cancer by Hepatic Artery Ligation and Infusion Chemotherapy

JOSEPH G. FORTNER, M.D., ROBERT J. MULCARE, M.D., ARIEL SOLIS, M.D., ROBIN C. WATSON, M.D., ROBERT B. GOLBEY, M.D.

From the Departments of Surgery, Diagnostic Radiology and Medical Oncology, Memorial Hospital for Cancer and Allied Diseases, New York City 10021

THE CONCEPT of treating primary and secondary liver cancers by an interruption of the hepatic arterial supply was suggested more than two decades ago.[12] The rational for this treatment is that both primary and metastatic tumors in the liver receive their blood supplies almost exclusively from the hepatic arterial system, with little contribution from the portal circulation.

This premise is supported by the following evidence: (1) numerous anatomical studies of both animal[1,3,16,17] and human[3,6,7,8,20] hepatic tumors using corrosive technics, dye injection and radiography, have verified nearly total arterial supply of liver cancer; (2) physiological blood flow studies in humans,[7] using radioactive xenon, demonstrate 90–95% decrease in tumor blood flow after hepatic artery ligation, as compared to 35% decrease in normal liver parenchyma; (3) in animal hepatic tumor systems, hepatic artery ligation produces selective necrosis of tumor in the liver, with increase in survival time[18]; (4) lastly, sporadic reports of inadvertant[13] or deliberate[11] hepatic artery interruption in humans with liver tumors indicate selective destruction of tumor without damage to the liver parenchyma.

In recent years, several clinical series have appeared which utilize a deliberate ligation of the hepatic artery for the treatment of primary and secondary tumors of the liver. Plengvanit,[19] in 1966, reported this treatment in 40 patients, all with primary liver cancer. Twelve showed an objective and/or subjective clinical response of 2 months or longer. A group in Sweden, represented by Nilsson[15] in 1966, and Almersjo *et al.*[2] in 1968, reported on a combined series of 11 patients with a variety of secondary liver tumors. They underwent hepatic artery ligation with division of falciform ligament, lesser omentum and hepatic diaphragmatic attachments. Some patients also received chemotherapy postoperatively. Seven of the 11 patients in these two reports were felt to have significant clinical improvement. One patient died of liver failure 3 days after the procedure. In four cases, selective tumor necrosis was documented at autopsy or re-operation. Murray-Lyon *et al.*,[14] in 1970, reported on a group of 10 patients with secondary hepatic tumors treated by hepatic artery ligation, with and without cytotoxic drugs. All showed clinical improvement defined as decrease in pain and increase in weight. In two of these cases, liver biopsy documented selective necrosis of tumor tissue after ligation.

This paper reports our initial experience with hepatic artery ligation in the treatment of primary and secondary liver cancers in humans.

Case Material

Twenty-three patients with primary and metastatic liver cancers underwent hepatic artery ligation (HAL). They ranged in age from 22 to 72, with an average age of 48.5 years. Twelve were men and 11 women. The range of tumor pathology is shown in Table 1. These include six with primary hepatocellular carcinoma, nine with colon or rectal carcinomas metastatic to liver, and seven patients with secondary liver tumors from a variety of other origins. Two patients with hepatocellular carcinoma, A.V. and L.S., had evidence of long-standing cirrhosis.

Table 1 also lists major surgical and chemotherapeutic treatments which the patients underwent before coming

---

Submitted for publication July 14, 1972.

TABLE 1. *Primary Pathology and Previous Therapy*

Primary Pathology	Patient	Sex	Age	Previous Therapy	
				Surgical	*Chemotherapy
Primary hepatocellular carcinoma	A.L.	F	57		5FU
	N.D.	F	37		I-A
	A.G.	M	42	Exploratory laparotomy—3 wks.	
	F.C.	F	36	Exploratory laparotomy—5 wks.	
	A.V.	M	22	Exploratory laparotomy—1 mo.	
	L.S.	M	39	Exploratory laparotomy—3 wks.	
Secondary colon carcinoma	W.L.	M	62	Ileocolectomy—10 mos.	5FU Cytoxan } O-O
	S.W.	F	73	Sigmoid colectomy—3 yrs.	
	F.S.	F	51	Abdominal-peritoneal resection—10 mos.	5FU O-O
	L.C.	F	53	Resection splenic fluxure—7 yrs.	5FU I-A
	Q.B.**	F	41	Sigmoid resection—3 yrs.	
	D.D.	M	53	Transverse colectomy—3 yrs.	5FU O-O
	W.J.	M	42	Sigmoid resection—11 mos.	5FU I-A
	M.C.	F	54	Descending colon resection—12 mos.	5FU I-A
	L.V.	F	50	Sigmoid resection—11 mos.	5FU O-A
Small cell carcinoma ? pulmonary	I.C.	M	52		
	R.B.	M	65		
Leiomyosarcoma (small bowel)	J.T.	F	32	Jejunal resection—2 mos.	Act-D Leukeran Methotrexate } O-O
Liposarcoma (back)	B.Y.	M	72	Excision—2 yrs.	
Pheochromocytoma	F.G.	M	51	Resection retroperitoneal mass—8 yrs. Resection recurrent tumor—1 yr.	
Carcinoid (ovary)	J.P.	F	32		
Mesothelioma ? multicentric	L. Dec.	M	62		Cytoxan Act-D O-A
Melanoma (ocular)	J.N.	M	38	Exploratory laparotomy—1 mo.	

* Chemotherapeutic clinical response classified according to Karnofsky *et al.*[9].

** ?Bile duct carcinoma.

to our insitution. In most of these patients other treatment modalities have either failed to palliate or offer little hope of doing so. It should be stated that a number of other patients were considered for hepatic artery ligation but that the procedure was not performed because of end-stage carcinomatosis with marked cachexia, debility or marginal hepatic function.

Clinical Protocol

All patients being considered for exploration for hepatic tumors undergo a full metastatic investigation. This includes complete radiographic and radioisotope surveys and biochemical profile including serum alpha-fetoglobulins, urinary catecholamines and VMA, and other special tests where indicated. Likewise, preoperative aortogram with superior mesenteric and celiac axis selective angiography is routinely carried out. This informs the surgeon of the exact configuration of the hepatic arterial supply. In addition, the patency of the intra- and extra-hepatic portal venous system must be proven before arterial ligation is undertaken. At the time of exploration, the surgeon has the fullest possible data profile of the patient's disease and need only evaluate the intra-abdominal and hepatic situation directly in order to make his choice of procedures.

The criteria for preoperative or intra-operative decision to perform HAL are as follows: (1) extensive cancer present elsewhere in the abdomen at laparotomy, so that partial hepatectomy or total hepatectomy and transplantation is not indicated; (2) when the major symptomatology is due to the hepatic disease, even though the patient is known to have tumor outside the liver preoperatively; (3) as the first step of a two-stage procedure, designed to decrease tumor bulk and destroy its ability to produce toxic substances, such as catecholamines, so that resection may be made feasible in an otherwise inoperable situation.

Operative Technic

The patients are explored through a bilateral subcostal incision in all cases. This allows maximum exposure, should hepatic resection be undertaken. If HAL is performed, the artery is ligated as close to the liver as possible. It is not uncommon that two or more arteries must be ligated, either because of congenital anatomic variations or local operative problems due to extensive tumor. Although sporadic and varying color changes in liver parenchyma and tumor were noted at the time of ligation, there was no consistent change in this regard by which the thoroughness or adequacy of the ligation could be judged intra-operatively. Cholecystectomy was performed in four patients because local tissue changes suggested ischemia. In the 19 other patients, no postoperative complication referrable to the gallbladder occurred.

In the 23 patients undergoing ligation, 17 had ligations of the common hepatic and gastroduodenal, and 10 of these also had catheters placed into the hepatic artery proper, via the gastroduodenal, for subsequent infusion of chemotherapeutic agents. In three patients the right and left hepatic arteries arose from separate origins and were ligated separately in each case. In one of these patients, infusion catheters were placed in both ligated arteries, and in another, a catheter was placed only in the artery feeding the lobe where the disease was dominant. In the third, no catheter was utilized. Another patient had three separate arteries feeding the liver. Each was ligated and no catheter employed.

Two other patients had normal arterial configurations but had ligation of the artery to only one lobe. In one of these cases, only the right hepatic artery was ligated because of the precarious preoperative condition of the patient, making common hepatic artery interruption unusually risky. The other patient had metastatic carcinoid in the liver, with florid symptomatology of the carcinoid syndrome. In this patient, only the left hepatic artery was ligated, because of concern that total arterial interruption would result in the massive release of 5-Hydroxytryptamine and other vaso-active components from the tumor. In this case, a catheter was placed in the right hepatic artery via the gastro-duodenal for infusion.

Nine patients in our series underwent only hepatic artery ligation, whereas 14 also had placement of a catheter for the infusion of chemotherapeutic drugs. When a constant infusion catheter[*] is to be utilized, it is placed in the distal artery after ligation. When feasible, this is done by ligation of the common hepatic and gastroduodenal arteries and the catheter passed into the common hepatic artery via the gastroduodenal. Intra-operative angiography through the catheter is performed to verify that the catheter is positioned so as to effectively infuse the tumor-bearing portions of the liver (Fig. 5). We chose to infuse via the artery rather than the portal system, because we felt that viable tumor cells both in the center and at the periphery of the ischemic tumor nodules could be reached by the arterial system without risking the thrombotic sequelae of an indwelling catheter in the portal system.

Postoperative Chemotherapy—Technic

A portable constant infusion pump with a 50 cc plastic reservior and delivering 6–10 cc per 24 hour period was used for infusion therapy.[**] Starting in the operating room, the catheters were infused with sterile saline until the postoperative condition of the patient was stabilized, at which time the chemotherapeutic agent was added. Chemotherapeutic agents were not used intra-operatively. In our series, infusion therapy lasted from 2½ to 10 weeks, as dictated by drug toxicity, clinical course, or technical difficulties with the catheters. The average duration of infusion was 5½ weeks, although catheters often were patent up to 5 months.

The chemotherapeutic agent administered by the catheter was chosen according to the histology of the tumor and preoperative response of the patient to systemic chemotherapy. The agents used are listed in Tables 3, 4 and 5. FUdr was used for metastatic colonic carcinoma unless a preoperative course of systemic 5FU had been administered. The concentrations in which FUdr is commercially available made it more convenient for the low flow and small reservoir characteristics of the pump. It was used in doses of 0.3 mg./Kg./24 hrs. Methotrexate, at 2.5 to 5 mg./24 hrs. total, was used in the colonic cancers where FUdr was not indicated, as well as in primary hepatomas, sarcomas and pulmonary carcinomas. Actinomycin-D was utilized in sarcomas and melanomas.

TABLE 2. *Postoperative Deaths and Complications*

Patient	Pathology	Procedure	Clinical Course
A.G.	Hepatocellular carcinoma	Common hepatic artery ligation	Died 11 days, hepatic coma
A.V.	Hepatocellular carcinoma	Common hepatic artery ligation, Methotrexate	Hepato-renal syndrome, Methotrexate toxicity, died P.O. day #7
L.C.	Colon carcinoma	Common hepatic artery ligation	Re-explored 2 wks.—colon perforation & GI bleeding, necrosis left lobe, died 10 wks.
J.P.	Carcinoid (ovary)	Left hepatic artery ligation, bilateral salpingo-oophorectomy	Died 2 wks.—pulmonary embolus
Q.B.	? Colon carcinoma ? Primary bile duct	Right hepatic artery ligation, FUdr infusion 3½ wks., T-tube common bile duct	Sepsis at 5 wks., re-explored at 16 wks. for obstructed left hepatic duct, I & D left lobe abscess, alive 29 wks.

---

[*] Intracath, 16 gauge, Deseret Co.

[**] The Sigmomotor Co., Model ML6.

TABLE 3. *Hepatocellular Carcinoma—Clinical Responses*

			Infusion Therapy			Duration Response		Current Status	
Patient	Sex	Age	Drug	Duration	Toxicity	Objective	Subjective	Alive	Dead
A.L.	F	57	MTX	5 wks.	none	38 wks.	38 wks.	44 wks.	
N.D.*	F	37	*5FU	10 wks.	none	16 wks.	none		30 wks.
F.C.	F	36	------ none ------			14 wks.	14 wks.		17 wks.
L.S.	M	39	------ none ------			none	none		5 wks.

* 5FU administered systemically

Because Actinomycin-D is selectively and rapidly taken up by hepatic cells, and because its cytotoxic effect is directly proportional to the dose of drug present in the tissue, it was delivered into the hepatic artery catheter in weekly bolus doses of 0.5 to 1.5 mg., rather than as a constant infusion. It is of interest that Actinomycin-D, given via the hepatic artery catheter, does not result in nausea or vomiting, as is invariably seen when the drug is given systemically. Another idiosyncrasy of this route of drug administration was the appearance of increase in liver enzymes during therapy in two patients, one on Methotrexate and one on Actinomycin-D. This phenomenon was reversible on cessation of the drug in both instances. It is preseumably a chemical hepatitis. Marrow and gastrointestinal toxicity can be seen with all drugs utilized.

Results—Clinical

The results of HAL in five of the 23 patients treated could not be accurately evaluated (Table 2). Four patients died in the postoperative period. Only one of these deaths was directly attributable to the ligation of the artery. This occurred in a 42-year-old man (A.G.), who had primary hepatocellular carcinoma with markedly deranged hepatic biochemistries preoperatively. He underwent ligation of the common hepatic artery and postoperatively showed a progressive deterioration of hepatic function, culminating in renal shutdown and death at 11 days. This was the only case in the series where death was clearly caused by the hepatic artery ligation.

The three other deaths were not apparently resultant from the arterial ligation. One patient (A.V.), with a primary hepatoma and cirrhosis, was started on Methotrexate, at 2.5 mg./24 hrs. total dose at the time of operation via a catheter in the ligated common hepatic artery. His immediate postoperative course was marked by hepatic decompensation and a hepato-renal syndrome with rising BUN. Despite stopping the Methotrexate after 4 days, he showed progressive signs of toxicity to the drug and died 7 days postoperatively in fulminant Methotrexate toxicity. In another patient (L.C.) with a metastatic colonic carcinoma, the postoperative course was marked by sub-hepatic absecess and upper gastrointestinal bleeding, each requiring re-operation. She died after 10 weeks. Throughout this lengthy period of multiple complications, her hepatic function was satisfactory. The fourth postoperative death was in the patient (J.P.) with symptomatic carcinoid syndrome. She died 2 weeks after ligation from a pulmonary embolus. Although she had shown moderate elevations in the liver biochemistries postoperatively, they were all improving at the time of death.

One patient (Q.B.) demonstrated a spectrum of pathologic change and a clinical course which also makes the evaluation of the effectiveness of the hepatic artery ligation unreliable (Table 2). This patient had signs of biliary obstruction and a past history of colonic carcinoma. On exploration there was an adenocarcinoma blocking the major bile ducts at the hilum. A T-tube was used to decompress the common bile duct. The pathologic structure was compatible with a primary biliary carcinoma or metastatic colon carcinoma. She developed sepsis and required re-exploration 16 weeks postoperatively to relieve a re-obstruction of the left hepatic duct and drain a left lobe abscess. She is alive at 29 weeks. Because of the obstructing nature of the liver tumor, and because of the complications of further obstruction and an abscess, it is not possible to assess the effect of the HAL in this case.

Eighteen patients were fully evaluated for periods of four to 41 weeks (Tables 3, 4, 5). Six had only hepatic artery ligation, while 11 had continuous infusion of chemotherapeutic agents via a catheter in the ligated artery. One patient with hepatocellular carcinoma (N.D., Table 3) received systemic 5FU after liga-

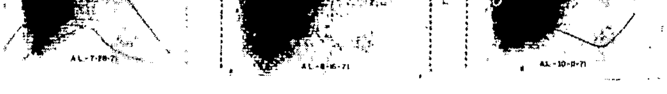


FIG. 1. Tc 99m sulfur colloid liver scan in patient A.L. with hepatocellular carcinoma. Left to right: Preoperative, 1 week and 8 weeks postoperative. Received constant infusion of Methotrexate for 5 weeks during which right lobe of markedly enlarged liver became non-palpable. Catheter angiogram (Fig. 5) showed that only right lobe was infused with drug.

TABLE 4. *Secondary Colon Carcinoma—Clinical Response*

			Infusion Therapy			Duration Response		Current Status	
Patient	Sex	Age	Drug	Duration	Toxicity	Objective	Subjective	Alive	Dead
W.L.	M	62	MTX	2½ wks.	+	none	none		18 wks.
S.W.	F	73	FUdr	5 wks.	–	21 wks.	23 wks.	25 wks.	
F.S.	F	51	MTX	3 wks.	+	none	12 wks.	23 wks.	
D.D.	M	53	MTX	3 wks.	+	none	none	5 wks.	
W.J.	M	42	------ none ------			26 wks.	26 wks.		50 wks.
M.C.	F	54	------ none ------			none	8 wks.		18 wks.
L.H.	F	50	------ none ------			none	18 wks.		30 wks.

tion. She had objective decrease in liver size for 16 weeks before "escaping" the therapeutic effect and dying at 30 weeks. For completeness, this case is included in Table 3, although the salutary effects of hepatic artery ligation cannot be distinguished from that of the conventional systemic 5FU therapy.

Three other patients also had primary hepatocellular carcinoma (Table 3). Two had ligation only. One (F.C.) had positive alpha-fetoglobulins and a febrile preoperative course attributable to the tumor. Postoperatively, she became afebrile and her serum alpha-fetoglobulins decreased. After 14 weeks, her disease again progressed, her alpha-fetoglobulins again increased, and she died at 17 weeks. The other patient (L.S.) showed no objective or subjective response to ligation, and died after 5 weeks of the disease. He had been cachectic, with far advanced disease at the time of operation.

One hepatoma patient (A.L.) had both ligation and postoperative infusion with Methotrexate for 5 weeks. She showed remarkable regression of liver size (Fig. 1) and enjoyed excellent health for a period of 38 weeks before signs and symptoms of advancing disease again became obvious. She was started on systemic Methotrexate and is alive at 44 weeks.

Seven patients who underwent HAL for metastatic colon carcinoma were evaluated. They are listed in Table 4. Three of these patients had ligation only. All had relief of pain for at least 8 weeks, and one also had a marked decrease in liver size and increase in weight and well-being over a 26-week period. Four other patients also received infusion therapy after ligation. Two of these four showed no response. One was a cachectic male (W.L.) with end-stage disease who succumbed to extra-hepatic disease after 18 weeks. He had failed the 5FU and Cytoxan therapy preoperatively and was infused with Methotrexate. The other patient (D.D.) failing to show a response also had failed 5FU preoperatively, and has shown no response to Methotrexate infusion 5 weeks after ligation. Two patients receiving infusion obtained good subjective relief of pain for 12 and 23 weeks, respectively. One of these (S.W.) also had a marked diminution in liver size with concomitant increase in weight for 21 weeks. These patients are alive at 23 and 25 weeks, respectively.

Seven other patients with secondary liver cancers of varying etiology have been adequately evaluated and are listed in Table 5. These included two probable pul-

TABLE 5. *Miscellaneous Secondary Cancers—Clinical Responses*

				Infusion Therapy			Duration Response		Current Status	
Patient	Pathology	Age	Sex	Drug	Duration	Toxicity	Objective	Subjective	Alive	Dead
I.C.	Small-cell ? pulmonary	52	M	MTX	3½	+	8 wks.	8 wks.		10 wks.
R.B.	Small-cell ? pulmonary	65	M	MTX	5	+	none	none		9 wks.
J.N.	Melanoma (ocular)	38	M	Act-D	3	–	none	5 wks.	5 wks.	
J.T.	Leiomyosarcoma (small bowel)	32	F	MTX Act-D	3	+	16 wks.	16 wks.	16 wks.	
B.Y.	Liposarcoma (back)	72	M	Act-D	10	+	17 wks.	17 wks.	17 wks.	
L. Dec.	Mesothelioma	62	M	Act-D	11	–	none	4 wks.		4 wks.
F.G.	Pheochromocytoma (retroperitoneal)	51	M	------ none ------			29 wks.	29 wks.	29 wks.	

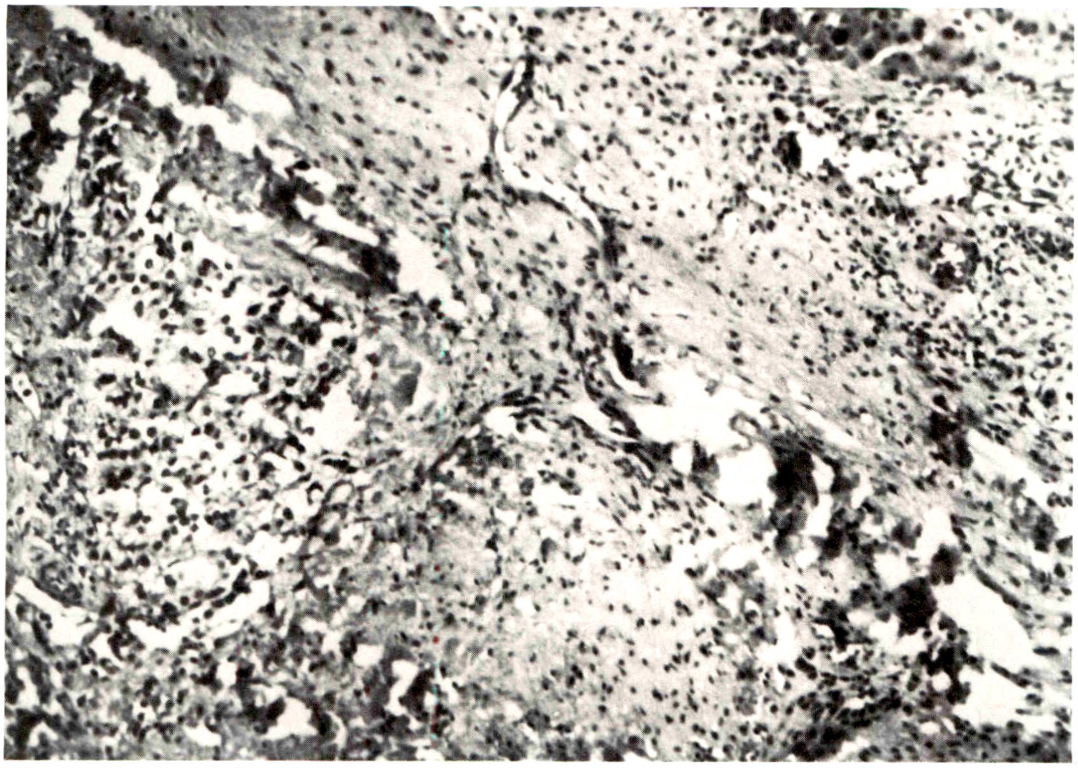


FIG. 2. Photomicrograph from operative specimen of nodule resected 15 weeks after hepatic artery ligation in patient F.G., with pheochromocytoma secondary in the liver. Normal liver parenchyma, upper right; necrotic tumor tissue lower center and lower left. Nest of some viable tumor cells left center (H&E ×50).

monary primaries, two soft parts sarcomas, a melanoma, a pheochromocytoma and a mesothelioma.

The patient with symptomatic pheochromocytoma (F.G.) had hepatic artery ligation only, as a first stage in a projected two-stage procedure. He became asymptomatic after 4 weeks and has remained so to date. He underwent reexploration at 15 weeks, with wedge resection of seven separate lesions of the liver. It is of note that all the resected tumor nodules were necrotic, many with a rim of viable tissue (Fig. 2). The surrounding liver parenchyma was normal. The patient is alive and well at 30 weeks. There are, however, other metastatic areas of disease in the abdomen, and he retains elevated blood levels for catecholamines.

The other six patients with secondary liver tumors of miscellaneous etiology all had infusion of chemotherapeutic agents subsequent to hepatic artery ligation. Two were small-cell carcinomas, presumably pulmonary in origin. Both had advanced hepatic tumors and demonstrable extra-hepatic disease preoperatively. Both received Methotrexate. One (R.B.) failed to show any objective or subjective response and died of the disease in 9 weeks. The other (I.C.) showed relief of right upper quadrant pain and diminution in liver size over an 8-week period before dying at 10 weeks of advanced generalized carcinomatosis.

Two other patients had soft parts sarcoma. One (J.T.) was a leiomyosarcoma of small bowel origin, who was

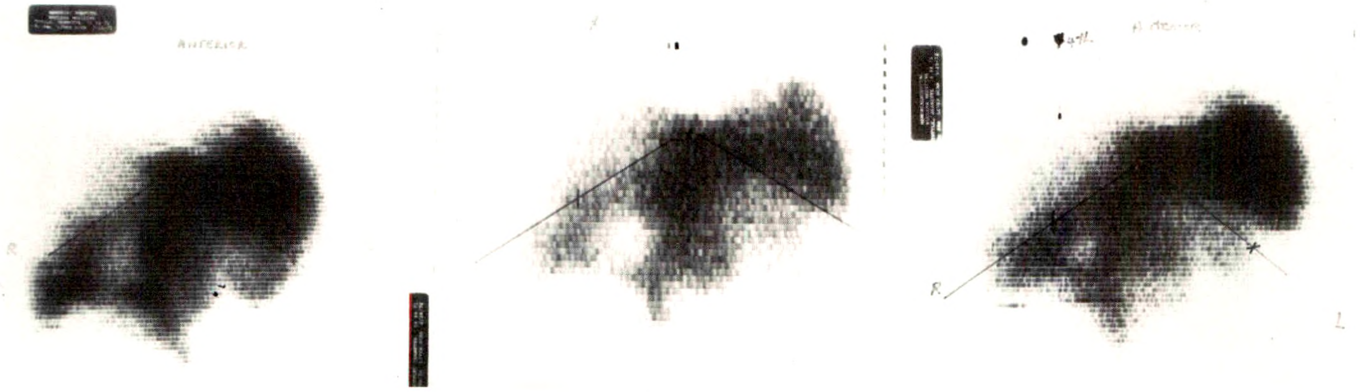


FIG. 3. Tc 99m sulfur colloid liver scan in patient J.T. with leiomyosarcoma secondary in the liver. Left to right: preoperative, 1 week and 12 weeks postoperative. During Methotrexate infusion liver size decreased markedly. Scan at 1 week shows little difference over preoperation. Scan at 12 weeks shows decreased liver size and "cold" nodules.

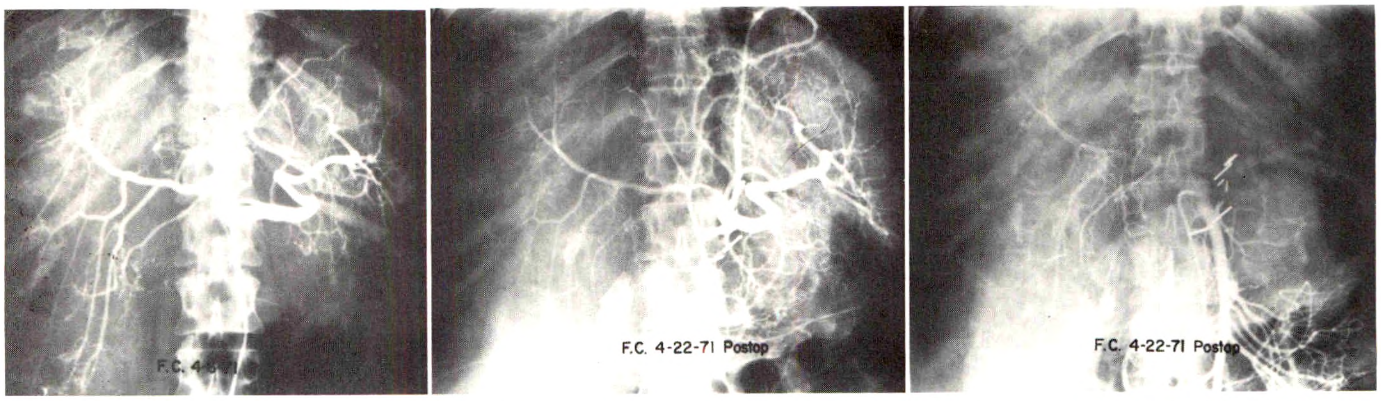


FIG. 4. Arteriograms in patient F. C. with hepatocellular carcinoma. Left: preoperative celiac arteriogram; middle and left, celiac axis and superior mesenteric arteriograms 1 week postoperative. Note collateralization of hepatic arteries via phrenic and retroduodenal vessels. This picture was constant in all patients studied.

re-explored at 14 weeks with the hope that a previously unresectable situation had converted to a resectable lesion. This was not the case. Indeed, despite a marked subjective and objective clinical improvement on Methotrexate infusion (Fig. 3), there was evidence of progression of disease at the time of re-exploration. She is well at 16 weeks. A liposarcoma from the back (B.Y.) showed remarkable objective and subjective response on Actinomycin-D which has lasted 17 weeks at this writing.

The one patient with melanoma secondary to a retinal lesion is alive at 5 weeks and has shown clinical diminution in pain for that period of time. He has received only two doses of Actinomycin-D, a week apart, at this writing.

The last patient in this group (L. Dec.) had a multicentric mesothelioma fully encasing and invading the liver. He died 4 weeks after hepatic artery ligation and Actinomycin-D therapy, but had experienced considerable relief of his right upper quadrant pain and right shoulder pain.

In summary of the clinical response, hepatic artery ligation was performed on 23 patients. In five, results could not be evaluated because of death or complications. They are listed in Table 2. Only one died of liver failure directly attributed to the ligation. Three other patients died in the early postoperative period of unrelated complications. One patient survived but with complications that make evaluation of the procedure impossible. Eighteen patients survived and were fully evaluated for 4 to 44 weeks. Eight are alive for an average of 20.5 weeks to date, 10 died at an average of 19.1 weeks post-ligation.

Thirteen of the 18 patients (72.2%) had significant relief of pain, most accompanied by an improved appetite and sense of well-being. The average duration of subjective improvement in these 13 patients is 16.8 weeks to date. Nine of the 18 (50%) had clear-cut objective signs of improvement including significant decrease in liver size, absence of preoperative tumor-associated fever, and weight gain. Thus far, the average duration of this objective improvement has been 20.5 weeks.

Four of these 18 patients (22.2%) showed no objective or subjective response, dying of their disease at an average of only 9.2 weeks postoperatively.

Twelve of the 18 patients received postoperative chemotherapy, 11 by constant infusion into a catheter in the distal ligated hepatic artery, and one systemically. Eight had subjective improvement for an average of 15.3 weeks, and six had objective improvement for 19.2 weeks to date. Three were failures.

Results—Pathophysiological

Extensive biochemical, radiographic and radioisotope studies were carried out in the postoperative period and compared with preoperative data in order to document the pathophysiologic effect of hepatic artery ligation on tumor and normal liver parenchyma.

Complete aortography and superior mesenteric and celiac angiography was done as soon postoperatively as possible in seven patients. In each of these studies, there was widespread collateralization of the arterial system via phrenic and retroduodenal vessels (Fig. 4). This probably occurs immediately after ligation. These collateral vessels have been documented in the same distribution and configuration in repeat studies at 6 weeks and 3 months in two of these patients.

Liver scans were routinely done when feasible in the first postoperative week and at subsequent periods when attempting documentation of clinical impressions. There was no distinct trend toward consistent postoperative changes in the scans. In a few cases it was possible to corroborate a clinically obvious decrease in liver size (Fig. 1, 3). One such case was a patient (A.L.) with hepatocellular carcinoma who underwent ligation after "escaping" from 5FU systemic therapy. She received Methotrexate by continuous infusion via a catheter in the ligated common hepatic artery. On this regimen, the right lobe of a massively enlarged liver became nonpalpable, while the left lobe remained unchanged. Repeat injection of radiopaque dye into the catheter at 6 weeks showed that only the right lobe was being perfused (Fig. 5). Serial Tc 99m liver scans done preoperatively at 1 week and 8 weeks documented this diminution in liver size and tumor mass (Fig. 1). She maintained this objective response together with weight gain and sense of well-being for 38 weeks before showing recrudescence of symptoms. She was started on systemic Methotrexate and is alive at 44 weeks.

Full biochemical profiles were followed closely in the postoperative period. The ranges and median values in 19 patients for bilirubin, alkaline phosphatase and SGOT are shown in Figure 6. Four patients are not included in these figures because in each, these values diverged widely from the medians due to unique clinical problems. These include the two patients (A.V. and A.G.) dying at 7 and 11 days with progressive deterioration in liver biochemistries, one patient (L.S.) with a chemical hepatitis from Methotrexate infusion at 10 days and one (Q.B.) in whom extra-hepatic obstruction was corrected at operation with choledochotomy. Despite a fairly wide range of values in the 19 patients charted in Figure 6, the median values indicate only a modest and transient rise in these biochemical parameters in the first few postoperative days. Marked biochemical evidence of deranged function was the exception.

Alpha-fetoglobulins were positive in two patients, both with hepatocellular carcinoma. In one (A.V.), dying of Methotrexate toxicity at 7 days, there was progressive decrease in the amount of the protein from ligation to the time of death. The other (F.C.), showed decreasing serum levels of alpha-fetoglobulins for 14 weeks post-ligation, but returned to preoperative levels at 14 weeks concomitant with signs of progression of disease.

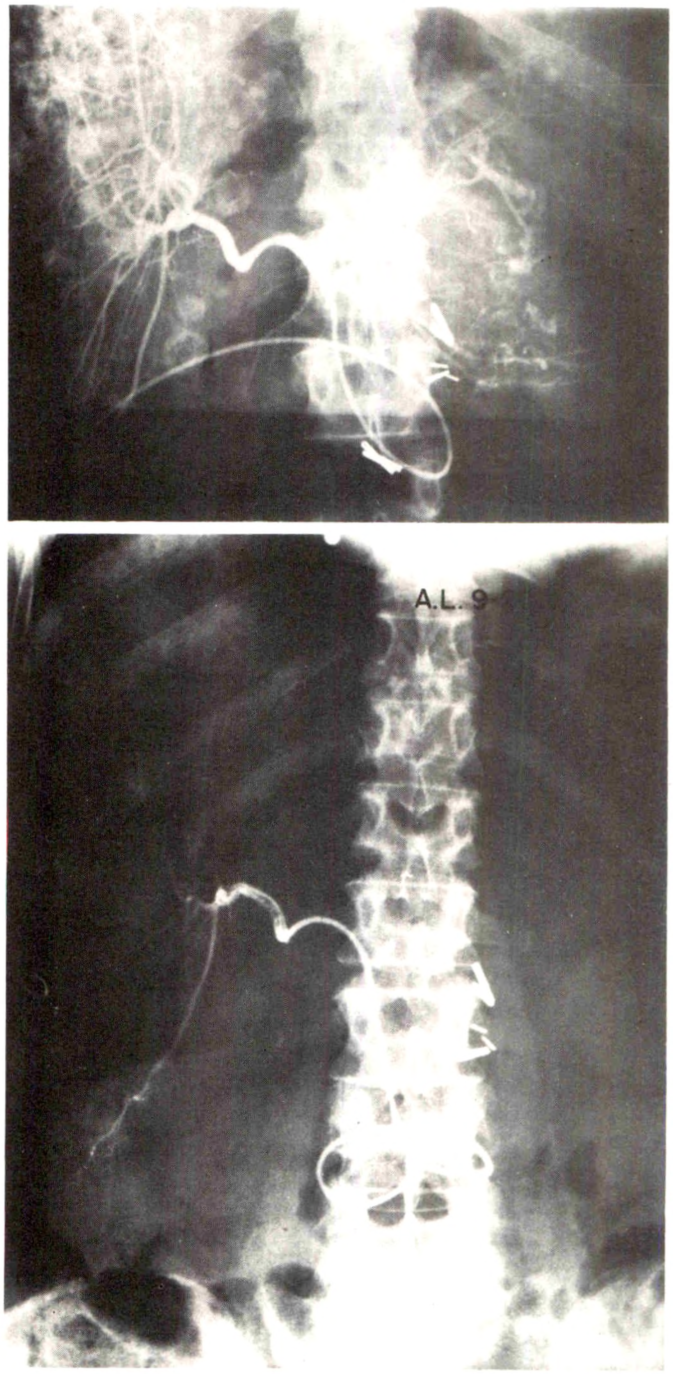


FIG. 5. Angiograms via catheter in ligated hepatic artery in patient A.L. with hepatocellular carcinoma. Top: operative angiogram—catheter effectively infuses all portions of the liver. Bottom: 6 weeks postoperative, in which only the vessels to the right lobe are patent.

Other biochemical parameters showed little tendency toward consistant changes after ligation. Uric acid levels, for instance, were markedly and progressively elevated postoperatively only in the patient who died at 7 days of Methotrexate toxicity and in the patient dying at 11 days in hepatic failure. Both presumably had massive damage to both hepatic and tumor cells. No consistent trends were traced in serum clotting factors, electrolytes or protein and glucose metabolism. Likewise, no consistent changes in the urinary parameters of creatinine, VMA, catecholamines or 5 HIAA occurred. This was true of the patients with pheochromocytoma (Table 5) and carcinoid (Table 2), despite the fact that they each had clinical remission of symptoms. The patient with pheochromocytoma (F.G.) had extra-hepatic, intra-peritoneal nodules of metastases which, no doubt, continued to produce catecholamines. In the patient with carcinoid (J.P.), it was elected to ligate only the artery to one of two involved lobes, thus leaving functioning tumor intact.

Among the most informative materials for studying

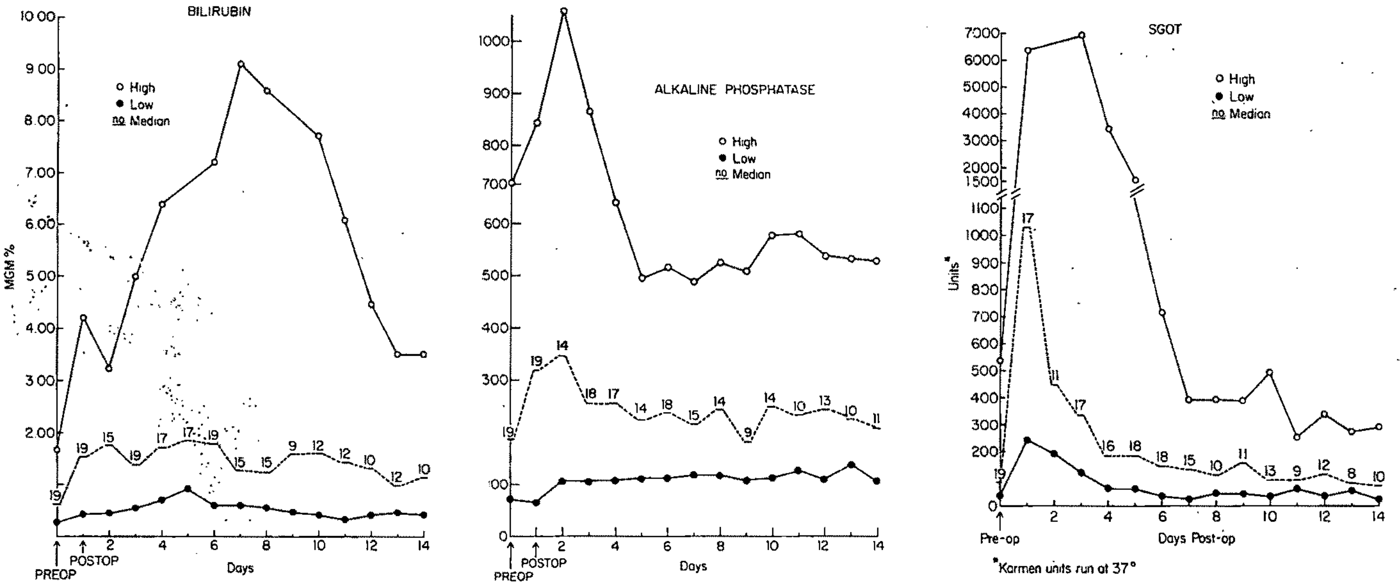


FIG. 6. Serum bilirubin, alkaline phosphatase and SGOT levels in 19 patients. High, low and median values for preoperative and first 14 postoperative days are indicated.

the pathophysiologic effects of hepatic artery ligation were tissue specimens. In five patients, we had the opportunity to study autopsy material or surgical specimens obtained at explorations subsequent to ligation. One patient (L. Dec.), autopsied 4 weeks after ligation, revealed extensive mesothelioma encasing and invading liver. Therefore, whether this was truly a liver tumor is questionable. There was focal necrosis of both parenchymal cells and tumor, as well as marked intravascular tumor growth. It is not clear whether the necrosis was due to intravascular tumor or to ligation.

In the other four cases, gross pathologic and histologic findings correlated well with arterial interruption. In three, there was clear-cut selective necrosis of tumor with preservation of parenchymal cells (Fig. 2). There was frequently a margin of viable tumor cells at the periphery of the nodules (Fig. 7). One patient (L.C.) had total necrosis of both tumor and parenchyma of the left hepatic lobe at re-exploration 2 weeks after ligation. On review of her arteriograms, there was considerable obstruction of the intra-hepatic portal radicals by tumor. With portal circulation to that area compromised, arterial ligation resulted in complete infarction. The remaining liver functioned well until her death 2 months later of other complications, including enterocutaneous fistula, intra-abdominal abscess and GI bleeding.

Discussion

Hepatic artery ligation is a relatively safe procedure in the context of those patients with malignancy. Survival is assured if care is taken preoperatively to verify the patency of the portal system by angiography, and if ligation is performed before the disease process has been allowed to progress to the point of major impairment of hepatic function. Only one patient in our series died of hepatic failure secondary to ligation. This patient (A.G.) was intermittently obtunded preoperatively with serum bilirubin levels greater than 8.0 mg./100 ml. and serum alkaline phosphatase over 1500 units. Of the 21 other patients without extra-hepatic biliary obstruction (patient Q.B. excluded), the highest preoperative bilirubin was 1.66 mg./100 ml. and the highest alkaline phosphatase was 770 units (Fig. 6). In retrospect, it is clear that this patient was not a suitable candidate for the operation. In the published total clinical experience cited in the introduction of this report five deaths occurred in 58 patients. Two were clearly due to hepatic failure. This included one in Plengvanit's series.[19] The other, in Nilsson's report,[15] also had received a large dose of a chemotherapeutic agent injected into the hepatic circulation at operation. This seems an acceptable mortality in view of the advanced disease present in all these patients. From our experience, it can be said that ligation will be tolerated unless far-advanced hepatic decompensation has occurred, or the portal circulation is impaired.

In the patients tolerating the procedure, however, the immediate post-operative response was not predictable by any preoperative clinical or biochemical parameters. There was a deterioration of hepatic function in several patients with reasonably good preoperative function. There was no pronounced morbidity in other patients in whom some postoperative difficulties were predicted on the basis of preoperative biochemical or clinical evalua-

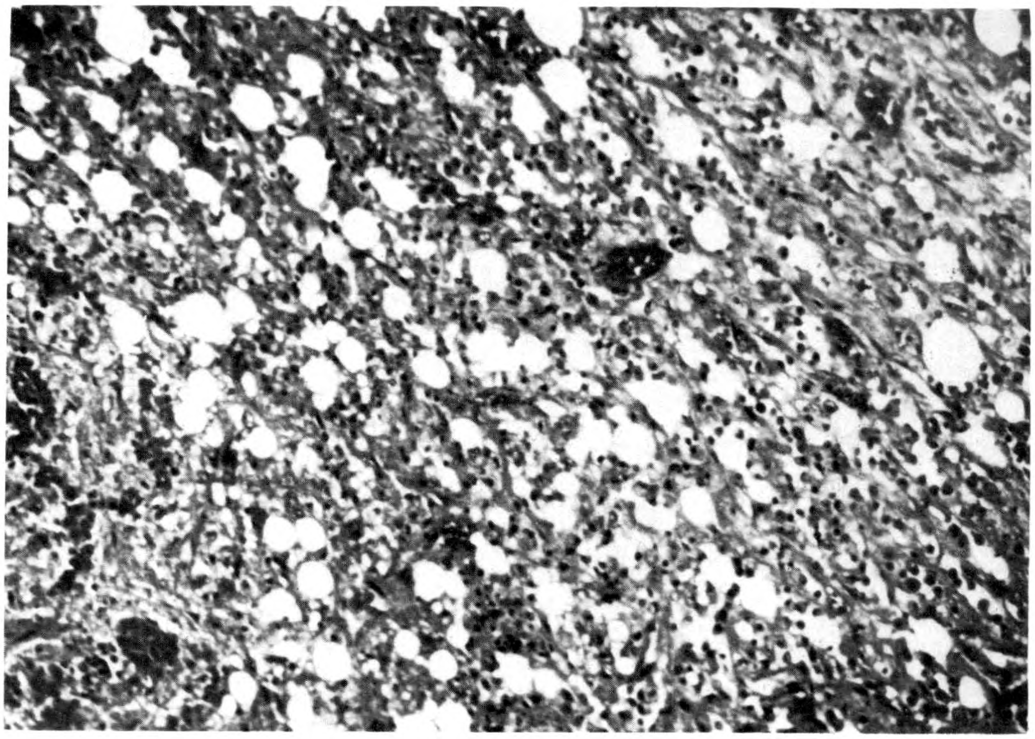


FIG. 7. Photomicrograph of autopsy specimen in patient J.P. with carcinoid secondary in liver. She died 14 days after hepatic artery ligation with pulmonary embolus. Fatty liver parenchyma center and upper right; necrotic tumor nodule lower left (H & E ×50).

tion. Because of this unpredictability of the immediate postoperative morbidity, we now allow sufficient time for recovery of hepatic and renal function to be well established before initiating infusion of chemotherapeutic agents. This usually starts at 6 to 8 days postoperatively. One patient (A.V.), with whom this rule was not followed, received Methotrexate starting immediately after ligation. His early postoperative course was complicated by hepatic and renal problems, the latter contributing to a florid Methotrexate toxicity resulting in his demise.

The data presented here, as in the other clinical series mentioned, suggest that HAL is not only safe, but is an effective palliative operation. Fourteen of 18 patients (77.8%) evaluated for 1 month or longer showed improvement (Tables 3–5). Eight had both subjective and objective changes, five showed only subjective change, and one patient (N.D.) had only objective signs of decrease in liver size without relief of subjective symptoms.

Only four patients failed to show any response. Each failure occurred in cachectic patients with far-advanced hepatic and extra-hepatic disease. All continued to deteriorate, and three have died at an average of only 10.6 weeks. It should be stressed that several patients with similar preoperative clinical pictures and laboratory profiles have received marked benefit from the procedure. Even in retrospect, there are no distinctive parameters by which one can predict which patient will be benefited by the procedure. However, the evidence suggests that palliation is better in duration and quality in the patient who undergoes ligation in reasonably good clinical condition and before major deterioration has occurred.

The composite of data obtained in our patients from the clinical courses, special studies and biopsy and autopsy material suggests the pathophysiologic effect of this operation. It seems likely that arterial interruption results in selective ischemia of the tumor cells. The viability of normal parenchymal cells is maintained by the portal circulation. This selective ischemia slows tumor growth rate and reduces the bulk of viable tumor through at least partial necrosis. The ischemia is transient, with surviving cells soon regaining full growth potential. The duration and effect of ischemia is probably dependent on the rate and efficiency with which effective arterial collateral circulation is established. Although postoperative angiography suggests immediate collateralization, this is probably not fully established for a period of days or perhaps weeks. Conolly *et al.*[4] have shown that dogs will survive afferent portal diversion 1 month after hepatic artery ligation, but not at 10 days after ligation. Croak *et al.*[5] studied eight dogs surviving end-to-side portacaval shunt 1 month after hepatic artery ligation. They noted radiographic and anatomic evidence of marked collateralization of the arterial system. These experimental data tend to corroborate our clinical impression of a transient period of arterial ischemia with subsequent re-establishment of full arterial supply and recrudescence of tumor growth.

In the series of patients presented here, attention has been directed toward potentiating the anti-tumor effect of the post-ligation ischemic period. For this purpose, infusion of chemotherapeutic agents into the ligated artery was carried out in 11 patients, and systemic chemotherapy in one. Statistical analysis is not applicable as yet because the numbers of patients involved and the period of effective palliation not yet completed in some, are small. But there is reason to be optimistic that combined ligation and infusion might prove more effective than ligation alone, at least in certain disease entities such as primary hepatoma and secondary sarcomas.

The results presented here were obtained in patients for whom conventional therapeutic modalities had failed, or offered little hope of palliation. The overall percentage of salutary response is 78%, with 50% obtaining remarkable remission of disease and symptomatology for significant periods of time. This study encourages the development and expansion of this form of treating primary and secondary liver tumors.

Summary

1. Twenty-three patients underwent hepatic artery ligation for symptomatic primary and secondary liver cancers. The indications, operation technic and clinical results are presented.

2. Thirteen of the patients also had postoperative chemotherapy to the liver via constant infusion into a catheter placed in the ligated artery at operation. The choice of drugs, technic and idiosyncracies of this route of drug administration are discussed.

3. One patient died of hepatic failure secondary to the ligation. Three other deaths were due to complications unrelated to arterial interruption. One patient's course was complicated by extra-hepatic biliary obstruction and could not be evaluated.

4. Eighteen patients were adequately evaluated for at least 1 month postoperatively. Seventy-eight per cent showed subjective relief of symptoms, and 50% had objective evidence of remission of hepatic disease. Only four (22%) patients failed to improve after operation.

5. Special pre- and postoperative studies were done and correlated with clinical data. The composite data suggest a pathophysiologic sequence of events resulting from ligation. These phenomena are discussed with reference to the technics presented here.

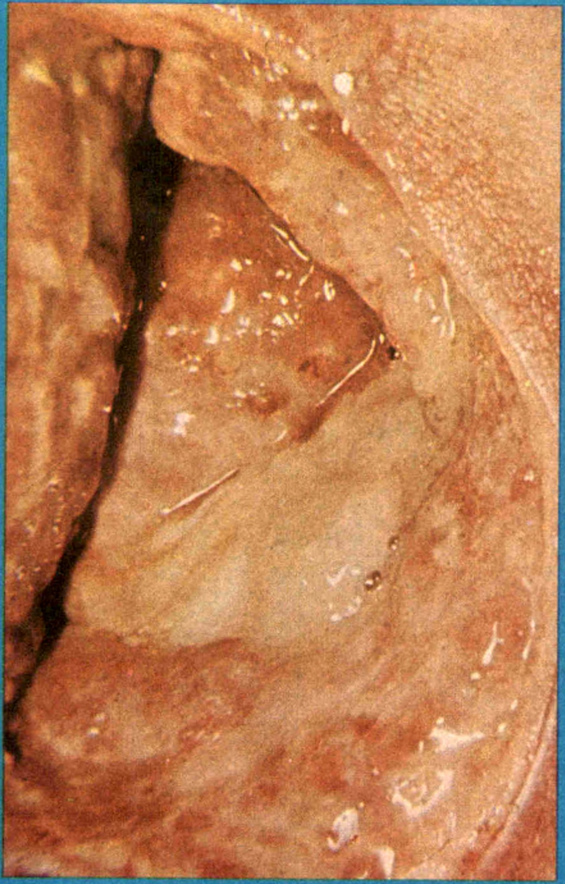
References

1. Ackerman, N. B.: Alterations of Intra-hepatic Circulation Due to Increasing Tumor Growth. (Abstract) Proceedings VII Congress European Society Experimental Surgery, p. 182, 1972.
2. Almersjö, O., Bengmark, S., Engevik, L., Hafström, L. O., Loughridge, B. P. and Nilsson, L.A.V.: Serum Enzyme Changes after Hepatic Dearterialization in Man. Ann. Surg., **167**:9, 1968.
3. Breedis, C. and Young, G.: The Blood Supply of Neoplasms in the Liver. Am. J. Path., **30**:969, 1954.
4. Conolly, W. B., Belzer, F. O. and Dunphy, J. E.: Safe Hepatic Artery Occlusion in Dogs. Surgery, **66**:772, 1969.
5. Croak, J. N., Paris, M. F. and Nance, F. C.: Studies of Hepatic Blood Flow and Hepatic Function after Ligation of the Hepatic Artery and Portal Vein. Am. Surg., **36**:724, 1970.
6. Gans, H.: Introduction to Hepatic Surgery. Elsevier Publishing Co., 1955, p. 232.
7. Gelin, L. E., Lewis, D. H. and Nilsson, L.: Liver Blood Flow in Man during Abdominal Surgery. II. The Effect of Hepatic Artery Occlusion on the Blood Flow through Metastatic Tumor Nodules. Acta Hepatosplenol. (Stuttg), **15**:21, 1968.
8. Healey, J. E., Jr.: Vascular Patterns in Human Metastatic Liver Tumors. Surg. Gynecol. Obstet., **120**: 1187, 1965.
9. Karnofsky, D. A., Ellison, R. R. and Golbey, R. B.: Selection of Patients for Evaluation of Chemotherapeutic Procedures in Advanced Cancer. Cancer Chemother. Rep., **16**:73, 1962.
10. Lewis, D. H., Nilsson, L. and Gelin, L. E.: Liver Blood Flow in Man at the Time of Operation. Rev. Int. d'Hepatol., **16**:853, 1966.
11. Madding, G. F., Kennedy, P. A. and Sogemeier, E.: Hepatic Artery Ligation for Metastatic Tumor in the Liver. Am. J. Surg., **120**:95, 1970.
12. Markowitz, J.: The Hepatic Artery. Surg. Gynecol. Obstet., **95**:644, 1952.
13. Mori, W., Masuda, M. and Miyanaga, T.: Hepatic Artery Ligation and Tumor Necrosis in the Liver. Surgery, **59**: 359, 1966.
14. Murray-Lyon, I. M., Parsons, V. A., Blendis, L. M., Dawson, J. L., Rake, M. O., Laws, J. W. and Williams, R.: Treatment of Secondary Hepatic Tumours by Ligation of Hepatic Artery and Infusion of Cytotoxic Drugs. Lancet, **2**:172, 1970.
15. Nilsson, L. A. V.: Therapeutic Hepatic Artery Ligation in Patients with Secondary Liver Tumors. Rev. Surg., **23**:374, 1966.
16. Nilsson, L. A. V., Rudenstam, C. M. and Zettergren, L.: Vascularization of Liver Tumors and the Effect of Hepatic Artery Ligation. Bibl. Anat., **9**:425, 1967.
17. Nilsson, L. A. V. and Zettergren, L.: Blood Supply and Vascular Pattern of Induced Primary Hepatic Carcinoma in Rats. Acta Pathol. Microbiol. Scand., **71**:179, 1967.
18. Nilsson, L. A. V. and Zettergren, L.: Effect of Hepatic Artery Ligation on Induced Primary Liver Carcinoma in Rats. Acta Pathol. Microbiol. Scand., **71**:187, 1967.
19. Plengvanit, U., Limwonges, K., Viranuvat, V., Hitanant, S. and Chearanai, O.: Treatment of Primary Carcinoma of the Liver by Hepatic Artery Ligation, Preliminary Report of 40 Cases. Int. Assoc. for the Study of the Liver. Liver Research; translation of the Third International Symposium, Tokyo and Kyoto, 1966, Antwerp, Tijdschrift voor Gastroenterologie, p. 490, 1967.
20. Wright, D.: The Blood Supply of Newly Developed Epithelial Tissue in the Liver. J. Path Bact., **45**:405, 1937.

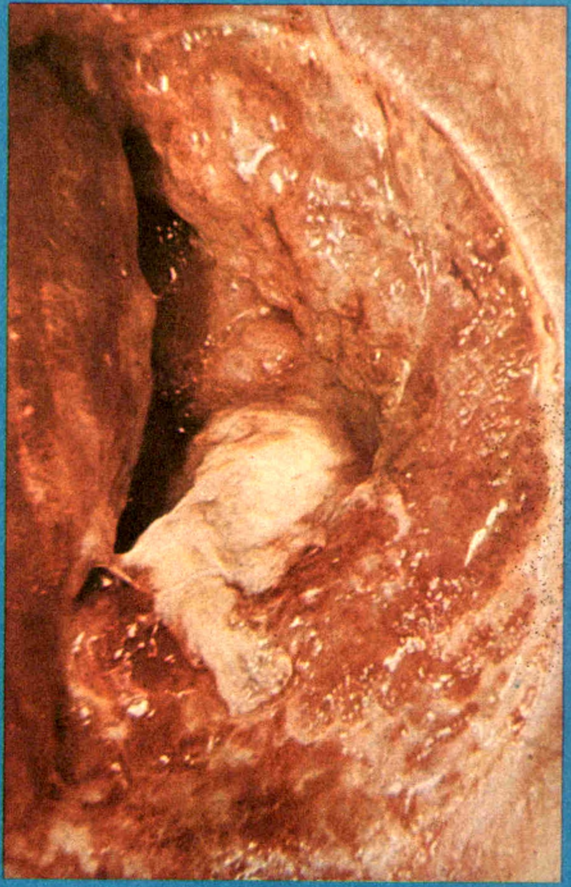
Decubitus Ulcers Yield to

Travase® Ointment

brand of **Sutilains**



Before treatment, necrotic matter coated the inner surfaces of this decubitus ulcer.



After six days of TRAVASE therapy, debridement is nearly complete and granulation evident.

Adjunctive Therapy—Observe Its Effects in 48 hours
When the recommended nursing technique is followed without deviation, this procedure can generate visible improvement within 48 hours of treatment. If no dissolution of slough occurs by then, further application is unlikely to be rewarding (recheck for break in procedure, usually due to use of cleansing or antiseptic agents which impair the effectiveness of the enzyme in TRAVASE).

Clinical observation and photos by Kathleen Brough Oldham, M.D., Marion County Home, Indianapolis, Ind.

Please see next page for prescribing information

First Class
Permit No. 39
Deerfield, Ill.

BUSINESS REPLY MAIL No Postage Stamp Necessary If Mailed in the United States

Postage Will Be Paid by Addressee

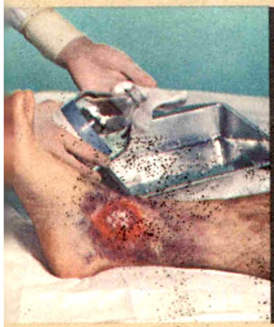
Flint Laboratories
Division of Travenol Laboratories, Inc.
200 Wilmot Road
Deerfield, Illinois 60015

Travase® Ointment brand of Sutilains

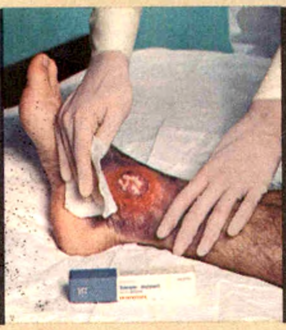
APPLICATION TECHNIQUE: TRAVASE Ointment is indicated as an adjunct to established methods of wound care for biochemical debridement. It dissolves and facilitates the removal of necrotic tissues and purulent exudates.

TRAVASE enzymes are selective. Virtually inactive on viable tissue.

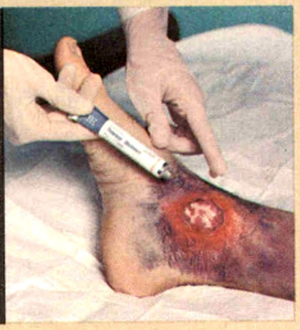
When this recommended nursing technique is followed without deviation, this procedure can generate visible improvement within 48 hours . . .



(Ulcer being irrigated) Thoroughly cleanse and irrigate the wound area using **only** sterile water or sodium chloride solution. Be sure to cleanse the wound of any antiseptics or heavy-metal antibacterial agents which may interfere with the enzyme activity.

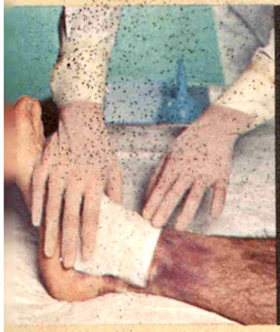


Thoroughly soak the wound area. Where practical, tubbing or showering is suitable. Or wet soaks with gauze pads may be used. Remember to avoid chemical cleansing agents which may interfere with the therapy.

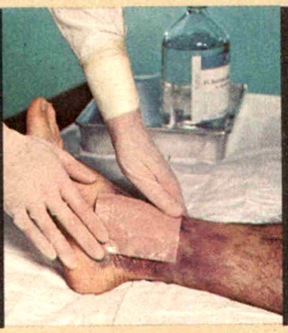


With a sterile cotton swab or finger cot, apply a very **thin** layer of TRAVASE Ointment. The ointment spreads easily and only a small amount is needed (a small dab of ointment will cover an area as big as the back of a hand).

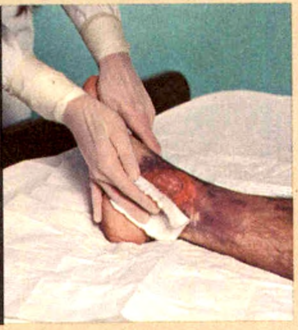
Be sure, though, to rub the ointment well into every crack or crevice of the wound and overlap the surrounding skin one-fourth to one-half inch beyond the area to be debrided—to be sure of complete coverage.



Apply loose, wet dressings, thoroughly soaked in sodium chloride solution or sterile water to the area to be debrided only.



Cover the moist dressings with an occlusive wrap (Saran wrap, Telfa Pads, or other plastic wrappings) to keep wound site moist. Do not extend occlusive wrap over ½ inch beyond area to be debrided.



When changing dressing, gently wipe away the dissolved material. Repeat the complete dressing procedure, including application of TRAVASE Ointment, four times daily.

The ulcer shown in these photos is simulated on a model in order to demonstrate the correct TRAVASE application technique.

To: FLINT LABORATORIES
Division of Travenol Laboratories, Inc.
200 Wilmot Road
Deerfield, Illinois 60015

Name ____________________

Title ____________________

Institution ____________________

Street ____________________

City ____________ State ____________ Zip ____________

Please send:

______Additional Information on TRAVASE® Ointment (brand of Sutilains)

______In-service training program

______Comment____________________

DESCRIPTION: TRAVASE® (brand of sutilains) Ointment is a sterile preparation of proteolytic enzymes, elaborated by **Bacillus subtilis**, in a hydrophobic ointment base consisting of 95% white petrolatum and 5% polyethylene. One gram of ointment contains approximately 82,000 casein units* of proteolytic activity.

ACTION: TRAVASE Ointment selectively digests necrotic soft tissues by proteolytic action. It dissolves and facilitates the removal of necrotic tissues and purulent exudates that otherwise impair formation of granulation tissue and delay wound healing (4).

At body temperatures these proteolytic enzymes have optimal activity in the pH range from 6.0 to 6.8.

INDICATIONS: For wound debridement (1,2)—TRAVASE Ointment is indicated as an adjunct to established methods of wound care for biochemical debridement of the following lesions:

Second and third degree burns,
Decubitus ulcers,
Incisional, traumatic, and pyogenic wounds,
Ulcers secondary to peripheral vascular disease.

CONTRAINDICATIONS: Application of TRAVASE (brand of sutilains) Ointment is contraindicated in the following conditions:

Wounds communicating with major body cavities,

Wounds containing exposed major nerves or nervous tissue,

Fungating neoplastic ulcers,

Wounds in women of child-bearing potential—because of lack of laboratory evidence of effects of TRAVASE upon the developing fetu

WARNING: Do not permit TRAVASE Ointment to come into contact with the eyes. In treatment of burns or lesions about the head or neck, shoulc the ointment inadvertently come into contact with the eyes, the eyes sho be immediately rinsed with copious amounts of water, preferably ster

PRECAUTIONS: A moist environment is essential to optimal activity of th enzyme. Enzyme activity may also be impaired by certain agents. **In vitro** several detergents and antiseptics (benzalkonium chloride, hexachlorophene, iodine, and nitrofurazone) may render the substrate indifferent to the action of the enzyme (3). Compounds such as thimeros containing metallic ions interfere directly with enzyme activity to a slight degree, whereas neomycin, sulfamylon-streptomycin, and penicilli do not affect enzyme activity. In cases where adjunctive topical therapy has been used and no dissolution of slough occurs after treatment with TRAVASE Ointment for 24 to 48 hours, further application, because of interference by the adjunctive agents, is unlikely to be rewarding.

In cases where there is existent or threatening invasive infection, appropriate systemic antibiotic therapy should be instituted concurrently

Although there have been no reports of systemic allergic reaction in humans, studies have shown that there may be an antibody response in humans to absorbed enzyme material.

ADVERSE REACTIONS: Adverse reactions consist of mild, transient pain paresthesias, bleeding and transient dermatitis. Pain usually can be controlled by administration of mild analgesics. Side effects severe enough to warrant discontinuation of therapy occasionally have occurre

If bleeding or dermatitis occurs as a result of the application of TRAVAS (brand of sutilains) Ointment, therapy should be discontinued. No system toxicity has been observed as a result of the topical application of TRAVASE Ointment.

Dosage and Administration

STRICT ADHERENCE TO THE FOLLOWING IS REQUIRED FOR EFFECT RESULTS OF TREATMENT

1. Thoroughly Cleanse and Irrigate Wound Area with sodium chlor or water solutions. Wound **MUST** be cleansed of antiseptics or heavy-metal antibacterials which may denature enzyme or alter substrate characteristics (e.g., Hexachlorophene, Silver Nitrate, Benzalkonium Chloride, Nitrofurazone, etc.).
2. Thoroughly moisten wound area either through tubbing, shower or wet soaks (e.g., sodium chloride or water solutions).
3. Apply TRAVASE Ointment in a thin layer assuring intimate cont with necrotic tissue and complete wound coverage extending to ¼ to ½ inch beyond the area to be debrided.
4. Apply loose wet dressings.
5. Repeat entire procedure 3 to 4 times per day for best results.

How Supplied

3P3002 TRAVASE Ointment is supplied sterile in one-half ounce tube (14.2 g.) containing 82,000 casein units of sutilains per gram hydrophobic ointment base.

The ointment must be stored under refrigeration at 2° to 10° C (35° to 50° F).

References

1. Garrett, T. A. **Bacillus subtilis** protease, a new agent for debridemen Clin. Med. **76:** 11-15, 1969.

2. Hesterberg, R. (Necrosis treatment on fermentative basis). Doctoral dissertation from the Chirurgical Clinic of the University of Munich. Dissertation Printing: Charlotte Schoen, Munich, 1964. (Ger.)

3. Howes, E. L. The healing of the burn may be hindered by its first ai therapy. 20th Cong. Soc. Inter. Chir., Rome, Italy, September 14-23, 19

4. Prytz, B., Connell, J. F., Jr., and Rousselot, L. M. **Bacillus subtilis** protease in the digestion of burn eschar. Clin. Pharmacol. Therap. **7:** 347-51, 1966.

---

*A casein unit is the amount of enzyme required to produce the same optical density at 275 mμ as that of a solution of 1.5 mcg. tyrosine/ml after the enzyme has been incubated with 35 mg. of casein at 37° C. one minute.

FLINT LABORATORIE
DIVISION OF TRAVENOL LABORATORIES, INC.
Morton Grove, Illinois 60053

Mediastinal Hyperfunctioning Parathyroid Tumors:

Review of 14 Cases

DONALD A. SCHOLZ, M.D., DON C. PURNELL, M.D., LEWIS B. WOOLNER, M.D.,
O. THERON CLAGETT, M.D.

*From the Mayo Clinic and Mayo Foundation,
Rochester, Minnesota 55901*

During the 43-year period from 1928 through 1970, approximately 1,000 patients with primary hyperparathyroidism were surgically treated at the Mayo Clinic. Not infrequently, hyperfunctioning parathyroid tissue was located in the superior mediastinum, often within the upper pole of the thymus gland, and was removed in the course of cervical exploration. Actual sternal splitting to expose the mediastinal structures was carried out much less frequently. In 14 cases, after one or more cervical explorations, the diagnosis of mediastinal hyperfunctioning parathyroid tumor was made after a sternal-splitting incision or at autopsy. The significant clinical, laboratory, and surgical findings in these 14 cases form the basis of this review.

Clinical Findings

The pertinent data on these 14 patients are summarized in the Table. The eight men and six women ranged in age from 27 to 57 years. The preoperative serum calcium values varied from 11.2 to 14.9 mg./100 ml. (normal, 8.9 to 10.1 mg./100 ml.). Renal calculi were present in 10 patients, roentgenographic bone disease of hyperparathyroidism was present in three patients, and no demonstrable osseous or renal complications were noted in four patients.

Surgical Procedures

The initial cervical exploration was carried out at the Mayo Clinic in nine of the 14 patients and elsewhere in five. Persistent hypercalcemia after the first cervical procedure resulted in a second cervical operation in five patients. In one patient (Case 9), the second cervical operation was performed as a third operation, that is, after removal of a large parathyroid tumor from the mediastinum.

Mediastinal surgery via a sternal-splitting approach was carried out at the Mayo Clinic in 11 patients, and elsewhere in 1 patient*; in the remaining two patients the mediastinal tumor was found at autopsy. The number of cervical parathyroid glands actually identified in previous cervical operations varied from 0 to 4. It is noteworthy that four glands were identified in the neck in five patients. Four patients had three glands identified, three patients had two, one patient had one, and in one other patient no gland was identified.

Pathologic Findings

A mediastinal tumor-like nodule, commonly called an "adenoma," was found in 14 patients. In five patients, an abnormality of one or more parathyroid glands was found on cervical exploration. We have not attempted to characterize these multiple gland enlargements as "chief cell hyperplasia," "mixed hyperplasia and adenoma," or "adenomatous chief cell hyperplasia."[5,9] In our opinion the present level of knowledge does not permit such an exact classification. Except for the carcinoma in Case 9, the mediastinal mass is referred to as a "tumor" (Table 1), whether or not one or more enlarged, apparently hyperplastic parathyroid glands also were removed from the cervical region.

The weight of tumor tissue removed from the mediastinum was recorded in 11 cases and varied from 500 mg. to 35 Gm. (average, 6 Gm.). The three tumors without

---

Submitted for publication July 3, 1972.

* Dr. B. F. L'Esperance—Two Harbors, Minn.

TABLE 1 *Mediastinal Hyperfunctioning Parathyroid Tumors (14 Cases)*

Case & year	Sex & age, yr	Presternotomy blood values, mg/100 ml			Osseous* lesions	Renal calculi	Findings on cervical explorations	Mediastinotomy
		Ca	PO_4	Urea				
1 1942	F 54	12.7 13.7	1.9 2.2	16	+	+	Parathyroid adenoma, excision & diagnosis ew (Nov. 1941). Re-explored at M.C. (July 1942): no parathyroid tissue	Chief cell tumor—5 Gm. (Oct. 1942)
2 1946	M 51	12.1 11.9	2.1 1.4	36	–	+	Two normal inferior glands (April 1946)	Chief cell tumor—1.7 Gm. (May 1946)
3 1949	M 41	13.6† 12.5	2.7 2.5	48	–	+	R. inferior—hyperplasia—180 mg.; other three glands normal on biopsy (Nov. 1949). Reexplored (June 1951): R. superior gland—hyperplasia—70 mg.; L. superior & inferior—normal	Autopsy (Jan. 1952): chief cell tumor (3 × 2 × 2 cm.)
4 1955	F 56	14.9 14.7	2.1 2.3	26	–	–	Exploration ew (March 1955): negative. Re-explored at M.C. (Apr. 1955): no parathyroid tissue	Chief cell tumor within pericardium—780 mg. (May 1955)
5 1959	M 32	11.8 11.2	2.5 2.7	30	–	+	All four glands normal (Jan. 1959)	Chief & oxyphil tumor—520 mg. (Nov. 1959)
6 1960	F 37	11.8 11.4	2.1 1.9	24	–	+	Exploration ew (Oct. 1959): three normal glands, L. inferior not found. Re-explored at M.C. (June 1960): no abnormalities	Chief cell tumor within thymus—500 mg. (June 1960)
7 1960	F 34	11.3 12.2	11.2 2.7	14	–	–	L. superior & inferior glands normal; R. thyroid lobectomy; parathyroid within thyroid—20 mg. (July 1959)	Chief cell tumor removed ew (0.6 × 0.8 × 0.6 cm) (Dec. 1960)
8 1960	M 38	. . .	. . .	. . .	–	–	Exploration ew (Oct. 1960): four normal glands; 1 excised	Autopsy: parathyroid carcinoma—35 Gm. (Oct. 1960)
9 1961	M 50	11.2 11.5	2.8 2.8	31	–	+	L. superior gland—hyperplasia—950 mg.; R. superior & inferior grossly normal; L. inferior not seen (July 1961). Re-explored (July 1963): R. inferior—hyperplasia, 120 mg.; R. superior—hyperplasia	Parathyroid tumor—2.3 Gm. (Nov. 1961)
10 1964	M 46	11.9 11.4	1.7 1.9	30	–	+	Three normal glands seen (Oct. 1963)	Cystic chief cell tumor—3 Gm. (Jan. 1964)
11 1967	M 49	14.2 14.4	1.7 1.7	41	–	+	L. superior gland—hyperplasia, 160 mg.; three other glands grossly normal (Sept. 1966)	Chief cell tumor—15 Gm. (March 1967)
12 1968	F 27	11.3 11.5	2.5 2.1	83	+	+	R. superior gland; L. superior—excised, normal; L. inferior glands not seen (May 1967)	Chief cell tumor within thymus—2.1 Gm. (March 1968)
13 1970	F 57	12.3‡ 11.5 11.6	3.0 2.0 2.7	Creatinine 0.75	–	–	Exploration ew (Dec. 1969): Four normal glands biopsied	Chief cell tumor within thymus (2.5 × 1.5 × 1.0 cm) (Nov. 1970)
14 1971	M 49	12.3 11.7	2.6 3.3	Creatinine 0.9	+	+	Chief cell "adenoma" of R. anterior mediastinum removed via neck incision; R. & L. superior—grossly normal; L. inferior not found (July 1970)	Chief cell tumor within thymus—920 mg. (Jan. 1971)
		Postop. cervical exploration						
		11.3§ 11.3	3.0	0.85				

---

* Defined as bone cysts, subperiosteal resorption of phalanges, or granular demineralization of skull.

† Postoperative values after second neck exploration.

‡ Serum iPTH by radioimmunoassay—390 μl eq/ml. (normal, 45 μl eq/ml.).

§ Serum iPTH 195 μl eq/ml.

recorded weights measured 0.8 to 3.0 cm. in diameter. Microscopically, all cell types were represented from predominantly chief cells to predominantly oxyphil cells, with frequent mixtures of cell populations. A rim of normal parathyroid tissue was rarely noted. The tumor was situated within the thymus gland or showed thymic tissue immediately adjacent in the majority of cases. One tumor was considered to be a carcinoma based on size of the cells, presence of mitosis within the tumor, and definite microscopic evidence of invasion of surrounding tissue.

The combination of a tumor in the mediastinum and abnormalities in one or more parathyroid glands in the neck was observed in five patients (Cases 1, 3, 9, 11, and 14). The pathologic findings in these patients are summarized in the following paragraphs.

In two patients (Cases 1 and 14) removal of a mediastinal tumor was preceded by the removal of a so-called adenoma from the neck at a prior operation. In Case 1 the tissue was not available for review; in Case 14 the cervical adenoma consisted of a tumorlike nodule approximately 1 cm. in diameter composed of chief and oxyphil cells with no rim of normal parathyroid tissue and showing little persisting fat within its substance.

In one patient (Case 3) an enlarged hyperplastic gland weighing 180 mg was removed at the initial cervical operation in November 1949 (Fig. 1*A*). Nineteen months later the remaining three glands were removed. These weighed 70, 30, and 20 mg., respectively, and at least two showed microscopic hyperplasia. Hypercalcemia persisted and mediastinal operation was advised but the patient refused further surgical treatment. At autopsy, performed elsewhere, a mediastinal parathyroid tumor measuring 3 by 2 by 2 cm. was demonstrated within the thymus gland (Fig. 1*B* and *C*).

In another patient (Case 9) one greatly enlarged gland (950 mg.) was excised on initial cervical exploration. Microscopic findings were those of hyperplasia. Two other parathyroid glands were considered to be of normal size and were not biopsied. One gland was not found. Four months later, the mediastinum was explored and a tumor weighing 2.3 Gm. was found within the thymus gland. The lesion was well circumscribed but contained some cells undergoing mitosis. Subsequent cervical exploration was carried out because of persistent hypercalcemia and two hyperplastic appearing glands were removed, the larger of which weighed 120 mg. Hypocalcemia, which required treatment with vitamin D and an oral supplement of calcium, then developed.

Initial cervical exploration in the fifth patient (Case 11) revealed a single enlarged gland (160 mg.), which was resected. Microscopically, definite parathyroid hyperplasia was noted (Fig. 2*A*). The other three glands were identified grossly and appeared normal. Six months later a 15-Gm. encapsulated tumor was removed from the mediastinum (Fig. 2*B* and *C*).

The patient with parathyroid carcinoma died suddenly and unexpectedly shortly after transfer to a Rochester hospital. Five days earlier a cervical exploration had been performed by his home physician. Four grossly normal appearing parathyroid glands were identified and one normal gland was excised. The patient's preoperative serum calcium values were in the range of 18 mg./100 ml. Because of persistent hypercalcemia he was transferred to the Mayo Clinic for further studies but unfortunately he died suddenly before any blood tests or roentgenograms were obtained. At autopsy, a tumor weighing 35 Gm. was found in the mediastinum. Microscopically, the tumor was composed largely of

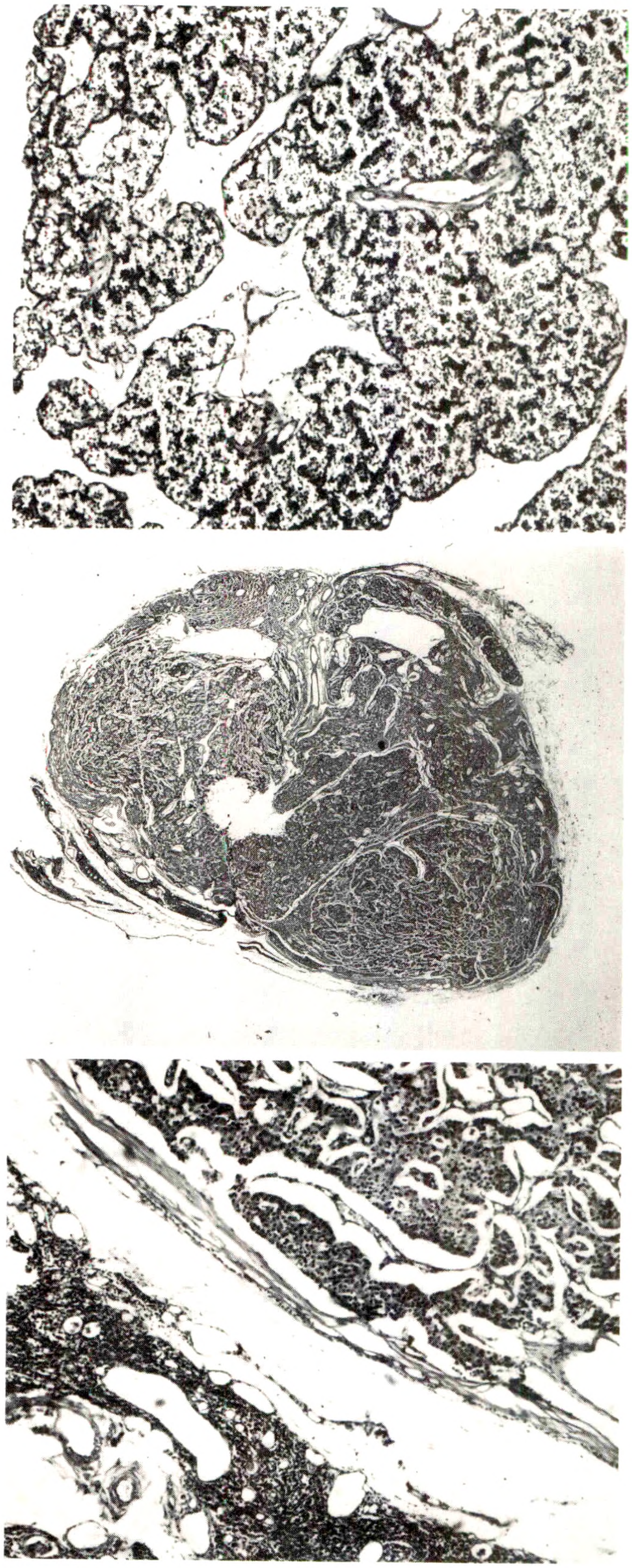


FIG. 1 (Case 3). *A*, Histologic section of large hyperplastic parathyroid gland (180 mg.) removed at cervical exploration. (H & E ×40.) *B*, Low-power section through mediastinal parathyroid tumor (3 cm. in diameter) found at autopsy in the same case. (H & E ×4.) *C*, Margin of tumor with rim of thymic tissue. (H & E ×40.)

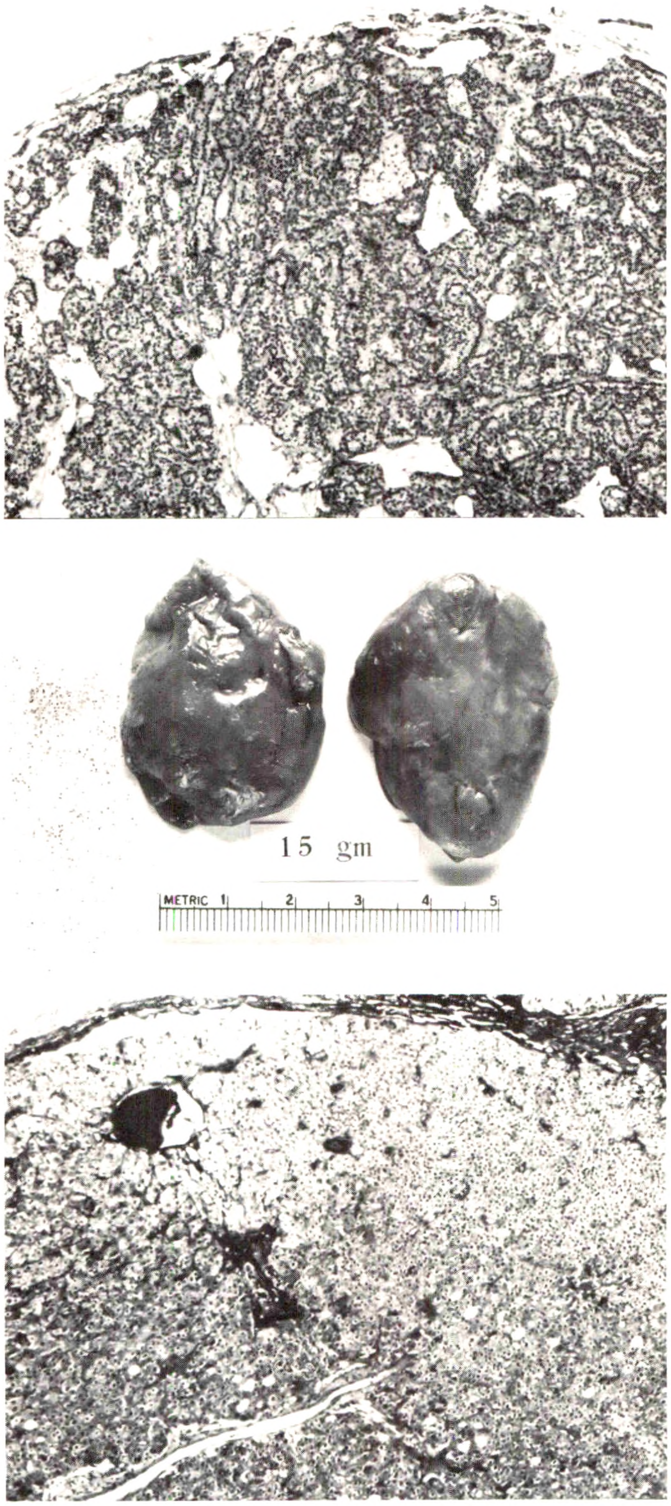


Fig. 2 (Case 11). *A*, Histologic section of hyperplastic parathyroid gland (weight, 160 mg.) removed at cervical exploration. Note diminution of stromal fat. (H & E ×40.) B, External and cut surfaces of 15-Gm. encapsulated parathyroid tumor removed from mediastinum 6 months after initial operation. *C*, Histologic section through margin of tumor showing numerous oxyphil cells. (H & E ×40.)

chief cells with considerable mitotic activity and invasion beyond the capsule. The pathologic diagnosis was parathyroid carcinoma.

Discussion

The variability that may exist in the number and anatomic positions of the parathyroid glands poses a challenge to the surgeon endeavoring to identify and excise hyperfunctioning parathyroid tumors. Gilmour[7] was able to identify four glands in 87% of 428 autopsies, five glands in 6%, and three glands in 6.1%. In a review encompassing 281 excised parathyroid adenomas, Norris[13] assigned cervical aberrant positions to 30 (10.7%), with 19 (6.8%) being located in the mediastinum.

In 1952, Castleman[3] stated that almost 20% of functioning adenomas excised at the Massachusetts General Hospital were located in the mediastinum. More recently, Nathaniels *et al.*[12] reviewed the cumulative experience at the same institution and reported a mediastinal parathyroid tumor in 84 (21%) of 400 patients with hyperparathyroidism. Pachter and Lattes[15] reported 98 parathyroid adenomas including two parathyroid adenomas occupying a mediastinal position. Hellström and Ivemark,[8] in a review of 138 cases of primary hyperparathyroidism, reported excision of five adenomas and two hyperplastic parathyroid glands from the mediastinum with autopsy findings of a mediastinal adenoma in one case in which a prior negative mediastinal exploration was reported. Mathisen and associates[10] documented four adenomas in the mediastinum in 59 proved cases of primary hyperparathyroidism.

The large number of mediastinal parathyroid tumors reported by Castleman[3] and Nathaniels *et al.*[12] may be explained by the fact that they included all tumors that could be removed by blunt dissection from the anterior or posterior mediastinal compartments through a cervical incision, as well as a sternal-splitting procedure, while others only reported the tumors to be mediastinal in location when sternal splitting was necessary to perform adequate exploration. In the series of Nathaniels *et al.*,[12] 19 tumors were removed by mediastinotomy.

The thymus and inferior parathyroid glands normally arise from the third branchial pouch. Their migration together into the anterior mediastinum is the cited embryologic explanation for the frequent finding of a parathyroid tumor attached to or embedded in the thymus gland. Cope[4] and Walton[18] have theorized that as a cervical parathyroid is replaced by tumor, its weight and the act of deglutition accelerate a downward migration, abetted by the negative intrathoracic pressure. Most mediastinal tumors are located in the anterior mediastinum, with 35% occurring in the posterior mediastinal compartment. Most posterior mediastinal tumors have been found in a superior position.[15]

Black and Utley[2] and Hoehn and associates[9] have stressed that the pathologic distinction between primary adenomatous chief cell hyperplasia and adenoma may be difficult. The spectrum of the gross and microscopic morphology of the parathyroid glands in such cases may be strikingly diverse. If all four glands are obviously hyperplastic (often to varying degrees), surgical removal of three glands and subtotal resection of the fourth gland usually restores the patient to a normocalcemic state, providing the remnant remains viable. Not infrequently, however, as in our cases, only one or two of the glands are enlarged at the time of initial exploration. The remaining glands appear grossly normal to the surgeon. When biopsy specimens from these "normal" appearing glands are examined under ordinary light microscopy, they often have been considered normal. Under these circumstances, it is not uncommon for hypercalcemia to persist, despite excision of the obviously hyperplastic tissue. However, even if the patient becomes normocalcemic after the initial operation, periodic reassessment is mandatory since hypercalcemia may recur. At a subsequent operation the remaining parathyroid tissue that initially appeared normal often shows evidence of hyperplastic changes as demonstrated in Case 3.

Preoperative studies to localize hyperfunctioning glands in the mediastinum, using selenomethionine (^{75}Se) as the radioisotope for scintiscanning[11] or selective arteriography,[6] were not performed in any of these patients. Selective cases in which isotope scanning has proved helpful in locating the site of the adenoma have been documented but, in general, the value of this technic has not been substantiated.[11] If a more specific agent for parathyroid gland tagging becomes available, this technic may be of more precise diagnostic help in tumor localization.

Beginning in April 1969, an immunoassay for serum immunoreactive parathyroid hormone (iPTH) became available for use in clinical study of patients with disorders of calcium metabolism.[1] Serum parathyroid hormone levels were available for the preoperative and postoperative assessment of our last two patients. The antiserum used in this assay often makes it possible to distinguish between iPTH present in the serum of patients with primary hyperparathyroidism and that of patients with hypercalcemia secondary to nonparathyroid malignancy.[17]

The finding of four normal parathyroid glands in the neck of one patient (Case 13) led to a suspicion of unrecognized malignancy. Extensive studies to exclude this possibility were conducted by the home physician with negative results. Significant elevation of the iPTH level was strong support for our recommendation for mediastinal exploration. In case 14 the persistence of hypercalcemia and a concomitant high level of serum iPTH after the removal of one cervical chief cell tumor, plus the identification of two normal cervical parathyroid glands, reinforced the probability that another functioning tumor was located in the mediastinum.

Efforts at localization of parathyroid tumors by selective venous catheterization with sampling of iPTH at various cervical and intrathoracic sites have been described by Reitz *et al.*[16] and O'Riordan *et al.*[14] Localization of tumors by this technic in a patient who has previously undergone a negative cervical exploration for hyperparathyroidism would be of great benefit to the surgeon.

Summary

The pertinent laboratory, roentgenographic, and surgical findings in 14 patients (eight men and six women) with mediastinal hyperfunctioning parathyroid tumors showed renal calculi in ten patients and roentgenographic evidence of bone disease of hyperparathyroidism in three; no osseous or renal complications were demonstrated in four patients. Twelve tumors were surgically excised through a sternal-splitting incision. Two tumors were ultimately found at autopsy but mediastinal exploration had not been performed in either patient. The combination of a tumor in the mediastinum and abnormalities in one or more parathyroid glands in the neck was observed in five patients.

A noteworthy finding is the fact that five of these 14 patients had five identified parathyroid glands, with four of the glands located in the cervical region.

Localization of hyperfunctioning parathyroid tissue by selective venous catheterization with sampling of iPTH at various cervical and intrathoracic levels would greatly assist the surgeon, especially in those patients who have had a negative cervical exploration or in whom a recurrence develops subsequently.

Addendum

Since this manuscript was submitted, hyperfunctioning mediastinal parathyroid tumors have been excised from three additional female patients. A 1.3 cm, calcified, cystic chief cell tumor was removed from one patient in whom four normal cervical parathyroid glands were identified. Three grossly normal cervical parathyroid glands were identified in the other two patients; a 6,000 mg. chief cell parathyroid tumor was removed from one and a 370 mg. chief cell parathyroid tumor was removed from the other. All three tumors were attached to thymic tissue.

References

1. Arnaud, C. D., Tsao, H. S. and Littledike, T.: Radioimmunoassay of Human Parathyroid Hormone in Serum. J. Clin. Invest., **50**:21, 1971.
2. Black, W. C., III and Utley, J. R.: The Differential Diagnosis of Parathyroid Adenoma and Chief Cell Hyperplasia. Am. J. Clin. Pathol., **49**:761, 1968.
3. Castleman, B.: Atlas of Tumor Pathology, Fascicle 15. Washington DC, Armed Forces Institute of Pathology, 1952.

4. Cope, O.: Surgery of Hyperparathyroidism: The Occurrence of Parathyroids in the Anterior Mediastinum and the Division of the Operation Into Two Stages. Ann. Surg., **114**: 706, 1941.
5. Cope, O., Keynes, W. M., Roth, S. I. and Castleman, B.: Primary Chief-Cell Hyperplasia of the Parathyroid Glands: A New Entity in the Surgery of Hyperparathyroidism. Ann. Surg., **148**:375, 1958.
6. Doppman, J. L., Hammond, W. G., Melson, G. L., Evans, R. G. and Ketchan, A. S.: Staining of Parathyroid Adenomas by Selective Arteriography. Radiology, **92**:527, 1969.
7. Gilmour, J. R.: The Gross Anatomy of the Parathyroid Glands. J. Pathol., **46**:133, 1938.
8. Hellström, J. and Ivemark, B. I.: Primary Hyperparathyroidism: Clinical and Structural Findings in 138 Cases. Acta Chir. Scand, Suppl., **294**:1, 1962.
9. Hoehn, J. G., Beahrs, O. H. and Woolner, L. B.: Unusual Surgical Lesions of the Parathyroid Gland. Am. J. Surg., **118**:770, 1969.
10. Mathisen, W., Muri, O., Jr. and Sander, S.: Primaer hyperparathyreoidisme. Nord. Med., **78**:1679, 1967.
11. McGeown, M. G., Bell, T. K., Soyannwo, M. A. O., Fenton, S. S. A. and Oreopoulos, D.: Parathyroid Scanning in the Human With Selenomethionine-^{75}Se. Br. J. Radiol., **41**: 300, 1968.
12. Nathaniels, E. K., Nathaniels, A. M. and Wang, C.-A.: Mediastinal Parathyroid Tumors: A Clinical and Pathological Study of 84 Cases. Ann. Surg., **171**:165, 1970.
13. Norris, E. H.: The Parathyroid Adenoma: A Study of 322 Cases. Int. Abstracts Surg., **84**:1, 1947.
14. O'Riordan, J. L. H., Kendall, B. E. and Woodhead, J. S.: Preoperative Localisation of Parathyroid Tumours. Lancet, **2**:1172, 1971.
15. Pachter, M. R. and Lattes, R.: Uncommon Mediastinal Tumors: Report of Two Parathyroid Adenomas, One Nonfunctional Parathyroid Carcinoma and One "Bronchial-Type-Adenoma." Chest, **43**:519, 1963.
16. Reitz, R. E., Pollard, J. J., Wang, C.-A., Fleischli, D. J., Cope, O., Murray, T. M., Deftos, L. J. and Potts, J. J., Jr.: Localization of Parathyroid Adenomas by Selective Venous Catheterization and Radioimmunoassay. N. Engl. J. Med., **281**:348, 1969.
17. Riggs, B. L., Arnaud, C. D., Reynolds, J. C. and Smith, L. H.: Immunologic Differentiation of Primary Hyperparathyroidism From Hyperparathyroidism Due to Nonparathyroid Cancer. J. Clin. Invest., **50**:2079, 1971.
18. Walton, A. J.: Surgical Treatment of Parathyroid Tumours. Br. J. Surg., **19**:285, 1931.

Patho-Physiological Changes Following Ischemia of the Spleen

M. J. TSAPOGAS*, M.D., R. A. PEABODY, Ph.D., A. M. KARMODY, M.B., Ch.M., F.R.C.S.E., F.R.C.S.Ed., C. CHUNTRASAKUL, M.D., H. GOUSSOUS, M.D., C. ECKERT, M.D.

From the Department of Surgery of Albany Medical College of Union University and the Veterans Administration Hospital, Albany, New York

THE SPLEEN has long been regarded as an organ of mystery and because in most patients splenectomy produces few apparent ill-effects, this organ has attracted little attention apart from the consequences of surgical trauma. Although splenectomy may produce little recognizable clinical effect, there is no doubt that patients should not be needlessly or routinely deprived of the functions of the spleen. Rare though well recognized thromboembolic complications, *e.g.* portal vein thrombosis, may occur after splenectomy and an increased incidence of infection has also been reported.[6,15]

When the splenic artery is used for visceral revascularization[2,9] splenectomy is generally carried out. The first aim of this experimental study was to determine whether splenectomy becomes inevitable after interruption of the splenic artery, which is not at present clearly known.

When splenectomy is difficult because the organ is large or there are perisplenic adhesions, as this is the case in some hematologic disorders, deprivation of the main arterial supply to the spleen may be a satisfactory alternative. This was the second aim of the present study. Finally in an attempt to further define the role and functions of the spleen, the study was designed to provide information on the pathophysiology of the partially or totally ischemic organ.

Methods

Splenic Artery Ligation

Two series of experiments were conducted. In the first series, 10 dogs underwent resection of a 2 cm. segment of the main splenic artery (Fig. 1). These experiments were so arranged that each dog served as its own control. Each animal was studied preoperatively, after the splenic artery was resected and again after splenectomy. Thus we reduced the number of biological variations that may occur among different groups of animals in which either splenectomy or splenic artery resection was performed. Routine hematologic studies were conducted on these animals, at weekly intervals for 8 weeks and on the fourth week the organs were surgically inspected and biopsies taken from areas which appeared abnormal and also from representative normal ones. Hematologic studies included estimation of hemoglobin, hematocrit, red cell count, white cell count and differential, platelet counts and measurement of Factors VIII and IX. The results were compared with those obtained from six animals which were submitted to immediate splenectomy.

Splenic Dearterialization

In the second series of experiments, the ability of the spleen to withstand total dearterialization was examined. In this series, complete dearterialization was achieved in six animals by ligation and division of the main splenic artery, the short gastric and all other arteries. The spleen was left attached only by the main splenic vein (Fig. 2). Samples for blood gases and pH were taken from this vein preoperatively and at hourly intervals for 4 hours after dearterialization. The operation was then terminated. Splenic scans were carried out preoperatively and at 1 and 4-month intervals post-

---

Submitted for publication July 26, 1972.

Request reprints Professor of Surgery, A.M.C.U.U., Chief, Surgical Services, VA Hospital, Albany, New York 12208.

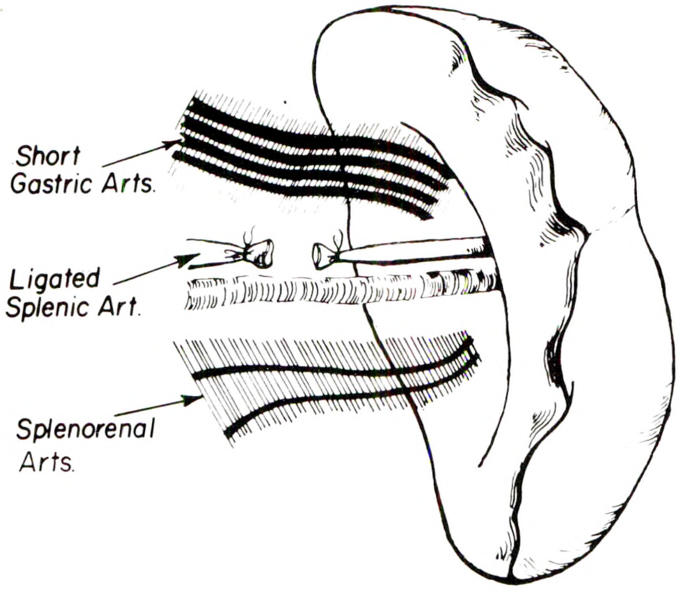


FIG. 1. Technic of ligation of splenic artery.

operatively. The organs were surgically reinspected 4 weeks later and appropriate biopsies taken for histologic examination. Removal of the spleen was done on the 16th week for full pathologic examination.

Red Cell Mass and Iron Turnover

Red cell mass was measured with autologous cells labeled with ^{51}Cr. Plasma iron turnover was calculated[8] from serum iron and ^{59}Fe measurements on blood drawn following injection of autologous plasma equilibrated with ^{59}Fe-labeled ferrous citrate.[13] Red cell iron turnover was calculated from the maximum uptake of iron in red cells and the red cell mass.[15]

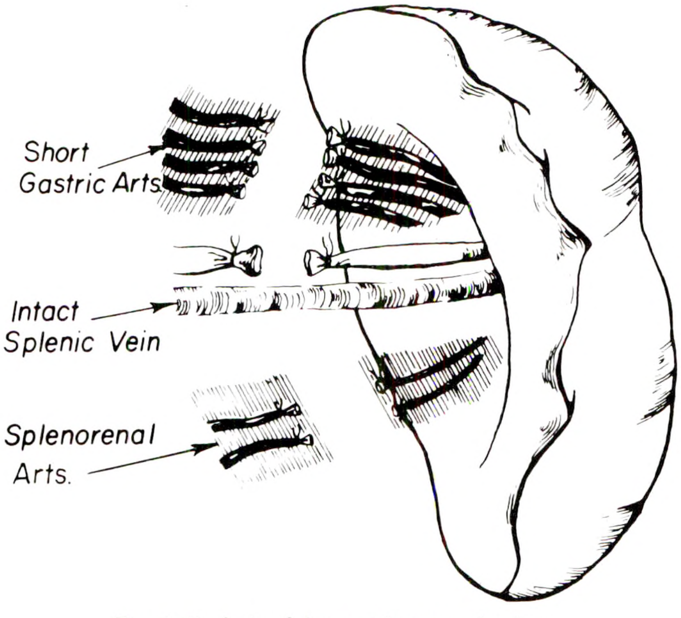


FIG. 2. Technic of dearterialization of spleen.

Factor VIII and IX Assays

These were done with canine plasma, deficient in one or the other factor, by a modified partial thromboplastin time assay.[5] Values were expressed as a percentage of the normal dog standard pool of 20 randomly chosen dogs (10 of each sex).

Platelet Labeling

Autologous platelets were labeled with ^{51}Cr by a method modified from Aster and Jandl.[1] They were concentrated by centrifugation of platelet-rich plasma (collected at 300g) and suspended in platelet poor plasma to form a concentration of 3×10^9/ml. One hundred microcuries of isotopic Na^{51}CrO$_4$ were then added to this suspension. After 1 hour at room temperature, 1 ml. of 1% ascorbic acid was added to halt the reaction. The labeled platelets were washed with platelet poor plasma and resuspended in 5 ml. fresh platelet-poor plasma before being injected into the dog. Platelets were counted by the method of Brecher and Cronkite.[3]

Platelet Sequestration

This was estimated with a scintillation crystal of 1⅞ in. diameter and a single channel analyzer spectrometer. Counts were taken over the spleen with 1¾ in. of lead collimation, with the probe perpendicular to the skin surface until equilibration occurred.

Splenic Scans

These were done with ^{99}Technetium Sulphur colloid preoperatively, one month after splenic artery resection and immediately before splenectomy.

Splenic Contractility

This was estimated by measuring surface counts over the spleen before and after the injection of 0.3–0.8 ml. of 1:10,000 adrenaline via a peripheral vein. Fifty per cent increases in pulse rate were taken as representing effective doses of adrenaline. Surface counts were measured under two different conditions. The first was done following red cell volume measurement with ^{51}Cr and the second after uptake of ^{51}Cr labeled platelets by the spleen.

Results of Splenic Artery Ligation

Hemoglobin

The changes in hemoglobin levels are shown in Figure 3. In the splenectomized group there was a steady fall over the 8-week postoperative period down to average levels of 14 Gm./100 ml. In animals with ligated arteries, the hemoglobin exhibited constant levels throughout, with little tendency to fall. When splenectomy was carried out in these animals the hemoglobin level again exhibited a tendency to fall progressively.

White Blood Cell Count

The changes in the white blood cell count are seen in Figure 3. The ligation series showed a sustained rise for the first 3 weeks which then subsided to normal. After splenectomy however, there was a sustained rise for 8 weeks and this pattern was also seen after primary splenectomy.

Platelet Count

The pattern of platelet counts is shown in Figure 3. In splenectomized animals, there was a marked and sustained platelet rise in the first 3 postoperative weeks. The counts then fell to more normal levels over the succeeding weeks. After arterial ligation, no marked change in the platelet count could be identified. In these animals when splenectomy was completed, the previously noted rise in platelet counts occurred for a period of 3 to 4 weeks postoperatively.

Factor VIII

After ligation of the splenic artery, there was a slight fall in the level of circulating Factor VIII. This was persistent over the eight week postoperative period, an average level of 80% of the normal standard being measured in these animals. Following splenectomy the levels of Factor VIII rose steadily with values approaching normal controls by the eighth postoperative week (Fig. 4).

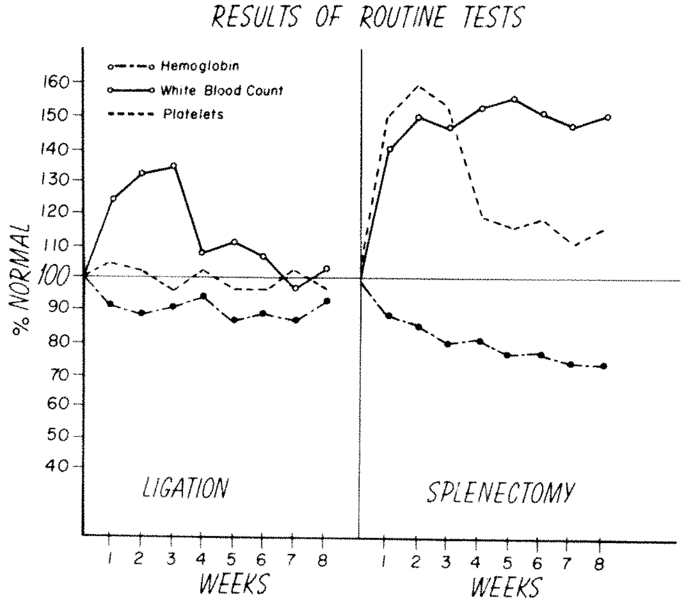


FIG. 3. Changes in hemoglobin, white blood cell and platelet counts following arterial ligation and splenectomy. Normal average values were hemoglobin 16.3 Gm./100 ml., white blood cell count 13,300/cu. mm., platelets 244,000/cu. mm.

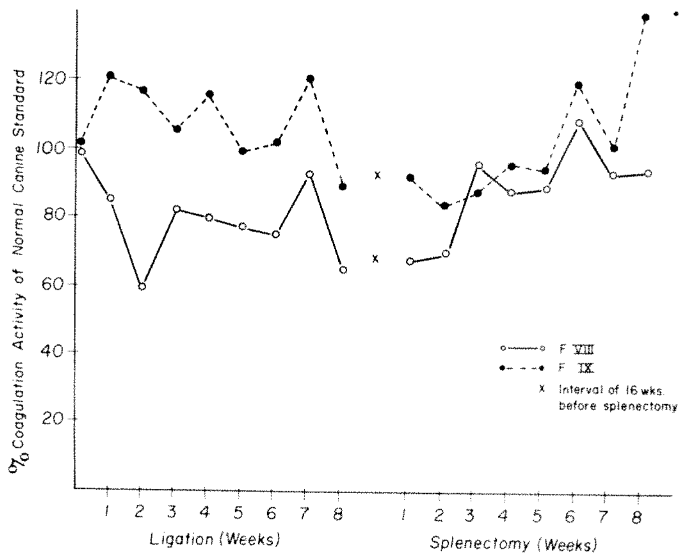


FIG. 4. Changes in Factors VIII and IX after arterial ligation and splenectomy. Mean values are shown. Standard Deviation: Ligation Series, 42–60%, Splenectomy Series, 23–52%.

Factor IX

Measurements of this factor revealed some fluctuation around normal values over the 8-week period after ligation. Following splenectomy there was a gradual increase in activity to values above the normal standard (Fig. 4).

Splenic Scans

Scans were carried out in each animal before ligation and at 4 and 16 weeks after arterial interruption. The changes are shown in Table 1. At 4 weeks, the scans remained unchanged in four animals (Fig. 5) and six showed a slight diminution in uptake. On the sixteenth week, three of the four normal scans remained unchanged while the fourth showed a slight loss of uptake. Of the six spleens which showed slight diminution in uptake at 4 weeks, only one had a further loss of uptake.

Red Blood Cell Mass and Iron Metabolism

Splenectomy caused a decrease of about 30% in the red cell mass compared to normal dogs ($p < 0.025$). Ligation of the splenic artery caused most of this decrease (26%). Similarly, ligation caused a significant

TABLE 1. *Results of Splenic Scans in Ligated and Dearterialized Animals*

	Ligation		Dearterialization	
Degree of Change	4th Week	16th Week	4th Week	16th Week
Normal	4	3	0	0
Minor	6	6	0	0
Moderate	0	1	2	2
Severe	0	0	2	2
No Function	0	0	2	2

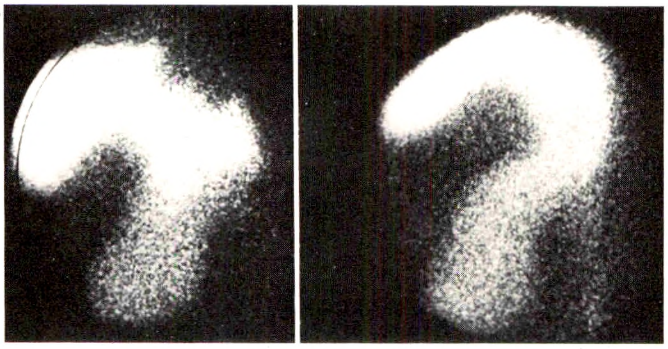


FIG. 5. Typical example showing similarity of splenic scans before and after arterial ligation.

drop, 38%, ($p < 0.025$) in the turnover rate of plasma iron and splenectomy resulted in a further decrease of 11%. Increases in the maximum amount of iron taken up by red blood cells following ligation appeared to offset the depressed plasma iron turnover since there was no significant change in the red cell iron turnover until splenectomy was performed (Table 2).

Splenic Contractility

Ligation of the splenic artery had no effect on the ability of the spleen to contract and discharge red cells in response to systemic adrenaline. However, the ability to discharge platelets was significantly decreased.

Platelet Sequestration

The sequestration of labeled platelets in the spleen was similar in normal animals and in those with an interrupted splenic artery. The rate of uptake, however, was slower in the ligation group. Representative data are shown in Figure 6. This figure also shows the dynamic response to adrenaline.

Histology

Examination of the spleens, both at the 4-week exploration and after splenectomy, revealed that the macroscopic appearances of the organs were essentially normal. Indeed on surgical exploration it was difficult to find by inspection abnormal areas for biopsy purposes. On histologic examination all biopsy and organ specimens exhibited a slight increase in the capsular thickening and fibrous stroma of the spleen. In four of the ten spleens, there were also small scattered areas of scarring mainly in the central areas of the organs. Apart from these minor changes the overall histologic appearances were little different from those of the normal organ. In general the small degree of histologic changes correlated well with the post-ligation splenic scans but in the single animal in which there appeared to be moderate deficiency in ^{99}Technetium uptake, the histologic changes were no worse than those seen in the other organs.

TABLE 2. *Effects of Artery Ligation and Splenectomy on RBC Volume, Plasma Iron Turnover and RBC Iron Turnover Changes in Red Cell Volume and Iron Metabolism*

Condition	RBC Volume (ml.)	Plasma Fe Turnover (mg./Kg./day)	RBC Fe Turnover (mg./Kg./day)
Normal	826	0.623	0.226
Post-ligation	*612	*0.384	0.233
Post-splenectomy	591	0.315	†0.198

* $p < 0.025$
† $0.2 > p < 0.4$

Results of Splenic Dearterialization

Surgical inspection 4 weeks after dearterialization showed that four of the six organs survived as recognizable structures. All of these organs exhibited surface scarring (Fig. 7) and in one, the central portion of the organ was completely replaced by fibrous tissue (Fig. 8). However, the polar regions appeared largely intact. The remaining two spleens were completely atrophic and one of these was the site of a small sterile abcess.

Blood gas and pH studies carried out on blood drawn from the splenic vein, at hourly intervals for 4 hours after dearterialization showed two distinct patterns. In those organs which survived, analysis showed that within the first hour there was metabolic acidosis, but this trend had stabilized or reversed by the end of 4 hours (Fig. 9A). Conversely, in those instances in which the spleen became atrophic, the measurements showed progressive uncontrolled metabolic acidosis (Fig. 9B).

In two of these animals, ^{125}I-labeled fibrinogen was administered immediately after dearterialization. Ten

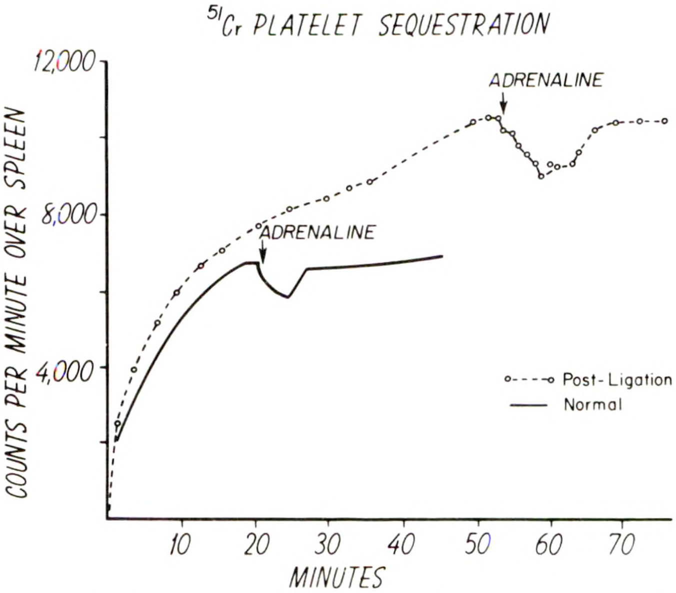


FIG. 6. Platelet sequestration after arterial ligation. The response of adrenaline is the same as that in normal animals. Data is uncorrected for differences in the amount of platelet radioactivity injected.

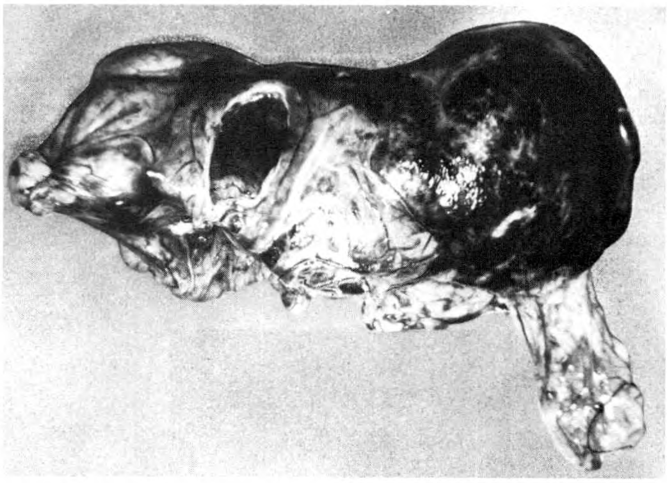


FIG. 7. Surface scarring and adherence of omentum in dearterialized spleen.

minutes later, blood drawn simultaneously from the splenic and renal veins showed equilibration of isotope between these sites. In a separate experiment this was repeated but the spleen was removed at the end of 3 hours. Counts per gram wet weight of tissue removed across the sectional area of the organ showed that radioactivity could be detected to the periphery (Fig. 10).

Splenic scans were carried out pre- and postoperatively on dogs undergoing splenic dearterialization (Table 1). The scans showed that at the end of the first postoperative month, two of the spleens had a moderate diminution in uptake and two showed a more severe disturbance in function (Fig. 11). In the animals with atrophic spleens, no sign of function could be demonstrated. The organs were excised at the end of 16 weeks and submitted to histologic examination. In each of the surviving organs there were easily recognizable areas of patchy fibrous scarring with preponderance of interspersed normal splenic tissue. It was also noted that the organs appeared to derive some degree of arterial supply by direct ingrowth from the omentum which was closely adherent to each of them.

Discussion

There is little published work on the changes which occur in the spleen after the splenic artery is ligated. This procedure has been considered for patients with portal hypertension and Banti's syndrome who could not tolerate extensive operation,[2] but its value was disputed by McFadzean and Cook[10] who found little benefit in five patients. Negligible gross and histologic changes in the spleen were noted[4] following ligation of the splenic artery in three dogs. However, no studies on hematologic or splenic function were conducted so that their conclusions are based on insufficient data from few experiments. By contrast, Sato[11] temporarily occluded the splenic arteries of dogs for periods up to 90 minutes and in 70% death occurred within 40 days after arterial flow was restored. In those dogs the spleens showed marked periarterial fibrous deposits and capsular thickening.

There has been therefore considerable doubt as to the type and extent of the changes which occur after interruption of splenic artery flow. It is important to have secure grounds for not removing the spleen after the use of the splenic artery for reconstructive arterial procedures. Our study was designed to investigate this matter. Comparison of the pre- and postoperative scans showed only small variations in organ size and function and this was confirmed by surgical and histologic examinations. The findings following the ligation of the splenic artery in the dog show clearly that this procedure does not significantly affect the structure of the healthy spleen.

The pathologic changes parallel the physiological

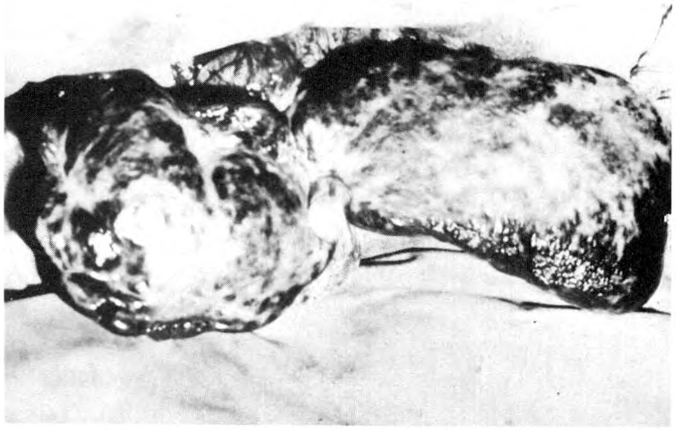


FIG. 8. Dearterialized spleen showing surface scarring and central necrosis

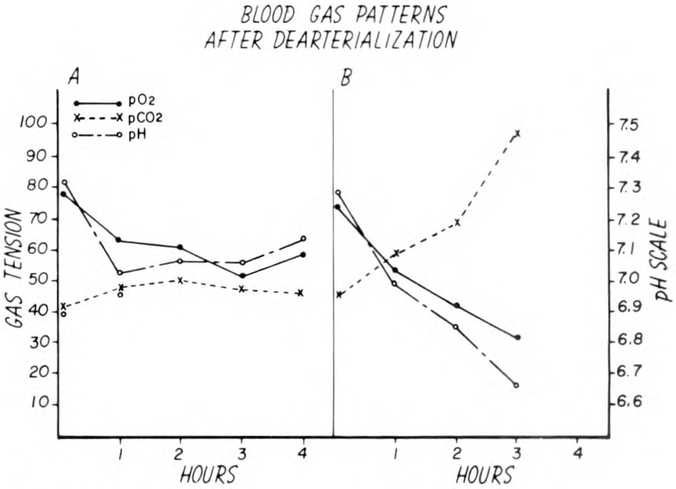


FIG. 9. A. Stabilization of blood gas patterns in surviving spleens. B. Increasing metabolic acidosis in non-surviving spleens.

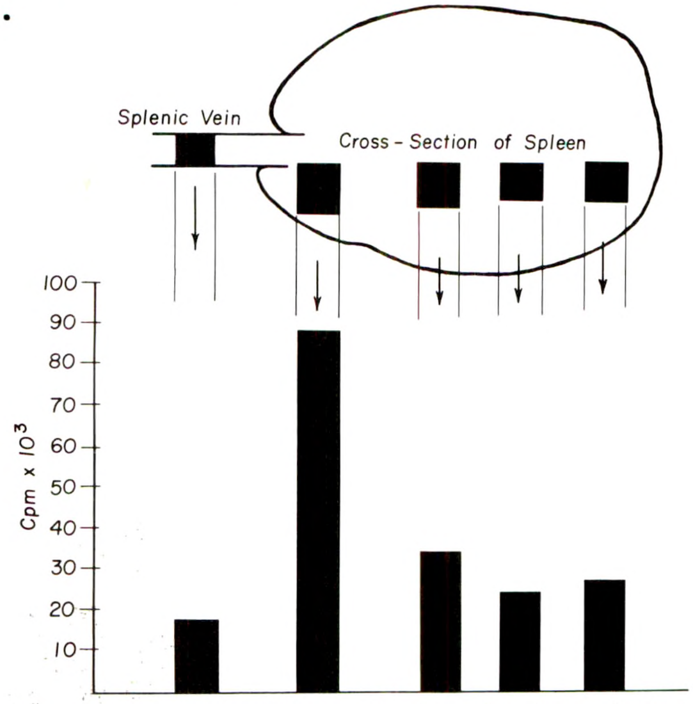


FIG. 10. Uptake of ^{125}I fibrinogen by spleen after dearterialization. Cpm/g wet weight is plotted for splenic areas shown in cross-section on the sketch.

findings; organ functions are well preserved after interruption of the main arterial supply. Compared with splenectomized animals, the ligation series exhibited little change in hemoglobin, white blood cell or platelet counts. By contrast however, there were signs of disturbance in splenic function as measured by changes in production of coagulation Factors VIII and IX. Such data provide further evidence for the role of the spleen in regulation of Factor VIII and IX levels,[5,14] but explanations for these observations remain unclear.

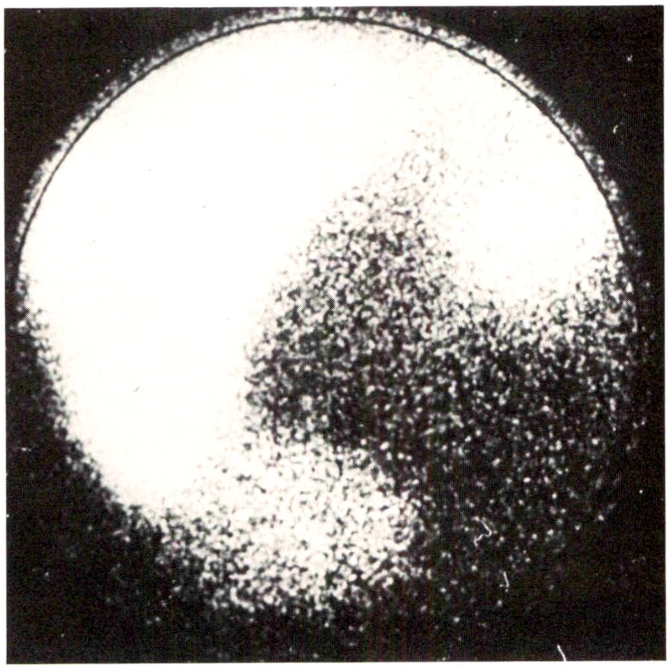


FIG. 11. Splenic scan of dearterialized spleen (shown in Fig. 8). The poles are functional while the central area is functionless.

In many animals the splenic capsule has marked contractile abilities in keeping with the role of the organ as a blood reservoir. The effect of noradrenaline on splenic contraction was reported in cats by Toghill and Prichard[12] using a method similar to that used in this study. The degree of contraction appears to differ for red cells and platelets but this may be due to greater damage to platelets than red cells in the labeled preparations used, resulting in greater retention of these damaged elements by the spleen. The similar effect of adrenaline on the contraction of normal dog spleens and those with ligated splenic arteries, indicates that the function of the splenic fibromuscular stroma is unimpaired by this degree of reduction of blood supply.

It was reported by Waldman[13] that splenectomy caused a 31% decrease in the circulating red cell volume. In these experiments, there was a similar fall after splenectomy (28%) but most of this occurred after ligation of the splenic artery. Similarly most of the decrease in plasma iron turnover observed between the normal dogs and splenectomized dogs, occurred following artery ligation. Consistent with these changes, the decreased red blood cell iron turnover following splenectomy suggests a decreased rate of red cell synthesis. Our findings in the splenectomized dog are in argeement with those of Waldmann. The depression of iron metabolism and red cell synthesis after ligation is interesting. This is probably due to subtle changes in splenic metabolism caused by the moderate ischemia of artery ligation and may also explain the slower rate of platelet sequestration observed.

Dalton and West[4] dearterialized the spleens in four dogs, the only intact attachment being the splenic vein. They reported that all of these organs survived in a practically normal state on gross and microscopic examinations. In our experiment four of six dearterialized spleens survived in recognizable form, but in each there was definite gross and microscopic evidence of ischemic fibrosis. Splenic scans confirmed that these organs retained a substantial degree of function. However, when the spleens underwent complete atrophy, the animals survived without apparent ill effects.

The experiments, therefore, confirm some of the conclusions of Dalton and West and show that the dearterialized spleen may retain a significant degree of function. Not all of the spleens were viable and in those which survived, the organs were not normal, but showed definite stigmata of ischemic damage.

It is indeed surprising that spleens do survive this degree of ischemia and the mechanism by which this occurs is of interest. In the immediate period after dearterialization the only means of blood supply to the organ is the splenic vein. Survival must therefore entail reflux into the spleen from the portal system. The blood gas and pH results shown in Figure 9A&B suggest that reflux may be established within the first 3 hours. This mechanism was confirmed with a radioactive tracer and its establishment reverses the initial metabolic acidosis which was exhibited in each instance. In the immediate postoperative period, however, the organs may derive a significant blood supply from the omentum which was found to envelop and be closely adherent to them (Fig. 7). These adhesions bled when cut and in two of the four organs, vascular connections between the omentum and the splenic tissue could be demonstrated on histologic examination. Over the long term, this was probably the source of blood supply which contributed most to the survival and function of the organs.

These experiments have shown conclusively that interruption of the splenic artery in the dog does not cause serious ischemic effects on the healthy spleen. Minor disturbances of morphology may be produced by this mechanism but survival of the organ with maintenance of its function can nevertheless be expected. The overall effect of arterial ligation on the animal's metabolism and homeostasis does not appear to be significant. It is therefore unlikely that this procedure would prove to be a satisfactory alternative to elective therapeutic splenectomy.

The experiments on splenic dearterialization demonstrated that the healthy organ has a great resilience under conditions of severe ischemia and a proportion of them may be able to continue to function even under these circumstances.

Summary

Splenectomy routinely follows the use of the splenic artery for revascularization of abdominal viscera. This may often be difficult to perform for correction of hematologic disorders and deprivation of the main arterial supply to the spleen may be a satisfactory alternative. Experiments were carried out in dogs to determine if ischemia of the spleen due to partial or total interruption of its blood supply makes splenectomy mandatory.

Ligation of the main splenic artery was carried out in 10 animals. Hematologic disturbances during an 8-week post-ligation period were minor compared with the effects following splenectomy in the same animals, but there was a significant decrease in red cell mass and plasma iron turnover in the post-ligation period with little further decrease upon splenectomy. Changes in Factor VIII and IX levels suggested that the spleen controls these factors. There was little histologic change after ligation of the splenic artery and scans and contractility of the spleen were similar in the normal and ligation groups.

In six animals the spleen was completely dearterialized and in four of these, the organ survived as a recognizable structure. Evidence that portal vein reflux contributed to their survival was obtained from radioactive tracer experiments and blood gas and pH measurements.

The experiments show that splenectomy is not mandatory after splenic artery ligation and that the spleen can survive even the severe ischemia of complete dearterialization.

Acknowledgments

We would like to thank Drs. M. Bishop and J. Jarmolych of the Department of Pathology for interpretation of histology specimens. Assays for Factors VIII and IX were kindly performed by Dr. W. J. Dodds. Also, we would like to thank Dr. R. Chodos and Nuclear Medicine Service for splenic scans. We would also like to thank Messrs. T. Halse and T. Thompson for skillful technical assistance and the Medical Illustration Service of the VA Hospital for the Figures.

References

1. Aster, R. H. and Jandl, J. H.: Platelet Sequestration in Man. I. Methods. J. Clin. Invest., **43**:843, 1964.
2. Blain, A. W. and Blain, A.: Ligation of the Splenic Artery, the Operation of Choice in Selected Cases of Portal Hypertension and Banti's Syndrome. Ann. Surg. **131**:92, 1950.
3. Brecher, G. and Cronkite, E. P.: Morphology and Enumeration of Platelets. J. Appl. Physiol., **3**:365, 1950.
4. Dalton, M. L. and West, R. L.: Fate of the Dearterialized Spleen. Arch. Surg., **91**:541, 1965.
5. Dodds, W. J., Raymond, S. L., Moynihan, A. C. and Fenton, J. W.: II. Independent Stimulators Regulating the Production of Factor VIII and IX in Perfused Spleens. J. Lab. Clin. Med., **79**:770, 1972.
6. Erickson, W. D., Burgert, E. O. and Lynn, H. B.: The Hazard of Infection Following Splenectomy in Children. Am. J. Dis. Child., **116**:1, 1968.
7. Gardner, W. J., Howe, R. F. and Olsen, D. D.: Aneurysm of the Hepatic Artery Treated by Exclusion with Splenic Artery Bypass. Am. J. Surg., **18**:947, 1969.
8. Huff, R. L. *et al.*: Plasma and Red Cell Iron Turnover in Normal Subjects and in Patients Having Various Hematopoietic Disorders. J. Clin. Invest., **29**:1041, 1950.
9. McCorristan, J. R. *et al.*:Splenohepatic Arterial Anastomosis for Aneurysm of Hepatic Artery. Surgery, **47**:636, 1960.
10. McFadzean, A. J. S. and Cook, J.: Ligation of the Splenic and Hepatic Arteries in Portal Hypertension. Lancet, **1**:615, 1953.
11. Sato, T.: Histological Changes in the Spleen Consequent on Circulatory Disturbance. Tohoku J. Exp. Med., **96**:281, 1968.
12. Toghill, P. J. and Prichard, B. N. C.: A Study of the Action of Noradrenaline on the Splenic Red Cell Pool. Clin. Sci., **26**:203, 1964.
13. Waldman, T. A., Weissman, S. M., and Berlin, N.: The Effect of Splenectomy on Erythropoiesis in the Dog. Blood, **15**: 873, 1960.
14. Webster, W. B., Zukoski, C. S., Hutchin, P., *et al.*: Plasma Factor VIII Synthesis and Control as Revealed by Canine Organ Transplantation. Am. J. Physiol., **270**:1147, 1971.
15. Weissman, S. M., Waldman, T. A. and Berlin, N. I.: Quantitative Measurement of Erythropoiesis in the Dog. Am. J. Physiol., **198**:183, 1960.
16. Whitaker, A. N.: Infection and the Spleen: Association between Hyposplenism, Pneumococcal Sepsis and Disseminated Intravascular Coagulation. Med. J. Aust., **1**:1213, 1969.

High Abdominal Aortic Aneurysm, Hepatic Artery Aneurysm, and Cystadenoma of Pancreas Treated Surgically in a Young Woman

BENJAMIN F. GIBBS, JR., M.D.,* DAVID R. JAMES, CDR., MC, USN, GARY D. KETRON, LCDR., MC, USNR, ROGER F. MILNES, CAPT., MC, USN.

From the Department of Surgery (Vascular Surgery Section) and the Clinical Investigation Center, U. S. Naval Hospital, San Diego, California 92134

MULTIPLE ANEURYSM FORMATION in systemic or visceral arteries characterized by atherosclerotic degeneration is well recognized. Nonatheromatous aneurysms occur less commonly, at times in association with other systemic diseases or connective tissue disorders.[1,4,5]

We recently encountered a young woman with nonatheromatous aneurysmal degeneration of the hepatic artery and abdominal aorta with an associated pancreatic cystadenoma. This constellation of findings and method of management are the basis of this report.

Case Report

A 48-year-old woman was admitted in March 1972, for evaluation of an enlarging asymptomatic abdominal aortic aneurysm associated with an hepatic artery aneurysm.

In 1963, following a hysterectomy, the patient was informed that the abdominal aorta was "slightly enlarged." She first became aware of a pulsatile abdominal mass in 1968, at which time an aortogram revealed a fusiform, apparently suprarenal aneurysm of the abdominal aorta with an associated hepatic artery aneurysm. Operation was not recommended. In June 1971, a repeat aortogram revealed no apparent change in the configuration of the two aneurysms (Figs. 1 & 1A). An ultrasonic echogram revealed the abdominal aortic aneurysm to measure 6 cm. in diameter. Repeat echogram in February 1972, revealed the diameter of the abdominal aortic aneurysm to have increased by 0.75 cm. leading to the present admission. Except for the presence of the pulsation, she remained asymptomatic. The patient had been treated for pulmonary tuberculosis several years previously with apparent cure.

On physical examination there was an easily palpable pulsatile mass in the left upper quadrant of the abdomen. Blood pressure and the remainder of the examination was normal. She was scheduled to undergo operation on March 20, 1972.

Laparotomy disclosed nonatheromatous aneurysmal enlargement of the common hepatic and proximal 2 cm. of right hepatic arteries. The distal right hepatic artery appeared normal. The left hepatic, left gastric, and splenic arteries were uninvolved. The superior mesenteric artery was large and its distal ramifications were tortuous. The right renal artery, arising from the aorta at about the same level as the superior mesenteric, was normal. The aortic aneurysm began at the level of superior mesenteric and right renal artery and ended proximal to the aortic bifurcation. There was no evidence of atherosclerosis. The left renal artery arose as two branches from the widest portion of the aortic aneurysm. An unsuspected finding was a firm, discrete, spherical mass, 3 cm. in diameter, within the body of the pancreas.

The spleen and body of the pancreas with its contained tumor were mobilized *en bloc* anteriorly. The pancreas was transsected through the neck, 4 cm. to the right of the tumor, preserving the splenic artery. The resected specimen was submitted for frozen section, and the pancreatic tumor was identified as benign cystadenoma. The stump of the remaining pancreas was closed with 3–0 Tevdec mattress sutures.

The common hepatic artery was divided at its origin and both ends were oversewn. The gastroduodenal artery was ligated at its junction with the hepatic artery aneurysm, and the right and left hepatic arteries were divided distally, totally excluding the hepatic artery aneurysm from the circulation. End-to-end anastomosis of splenic artery to right hepatic artery was performed using 6–0 vascular sutures. End-to-side anastomosis of left hepatic artery to splenic artery was accomplished using a similar technic. With release of the vascular clamps, blood flow was re-established through the splenic artery into both hepatic arteries.

The left renal vein was divided between clamps to facilitate exposure of the proximal extent of the aortic aneurysm. The aorta was clamped proximal to the superior mesenteric and renal arteries,

---

Submitted for publication July 5, 1972.

* Request reprints: 2290 Sixth Avenue, San Diego, California 92101.

The opinions or assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the Department of the Navy.

and transected immediately distal to the superior mesenteric and right renal arteries, but proximal to the left renal artery. A 19 mm. dacron graft was sutured to the proximal aortic cuff which held sutures poorly. Therefore, a 2-inch sleeve of the graft material was used to buttress the suture line with appropriate slits and apertures created in the buttress, to allow egress of the superior mesenteric and right renal arteries. The proximal occluding clamp was then placed distal to the right renal artery, restoring flow to the superior mesenteric and right renal arteries. Occlusion time for these two arteries was 14 minutes.

The left renal artery was detached from the aneurysm, preserving a 1 cm. radius cuff of aortic wall around the renal artery orifice. An ellipse was removed from the left anterior wall of the graft, and the left renal artery with its preserved cuff of aorta was reimplanted into the graft using continuous 4–0 vascular suture. The occluding clamp was repositioned distal to the reimplanted left renal artery, restoring flow to that artery after a total occlusion time of 24 minutes. The normal distal aorta was transected proximal to its bifurcation. Anastomosis of the graft to distal aorta restored blood flow to the lower extremities. The previously divided left renal vein was reanastomosed. The abdominal incision was closed without drainage.

On the evening of operation, re-exploration was necessary to control bleeding from a small artery on the aneurysm wall which had been left *in situ*. The postoperative course was otherwise uncomplicated.

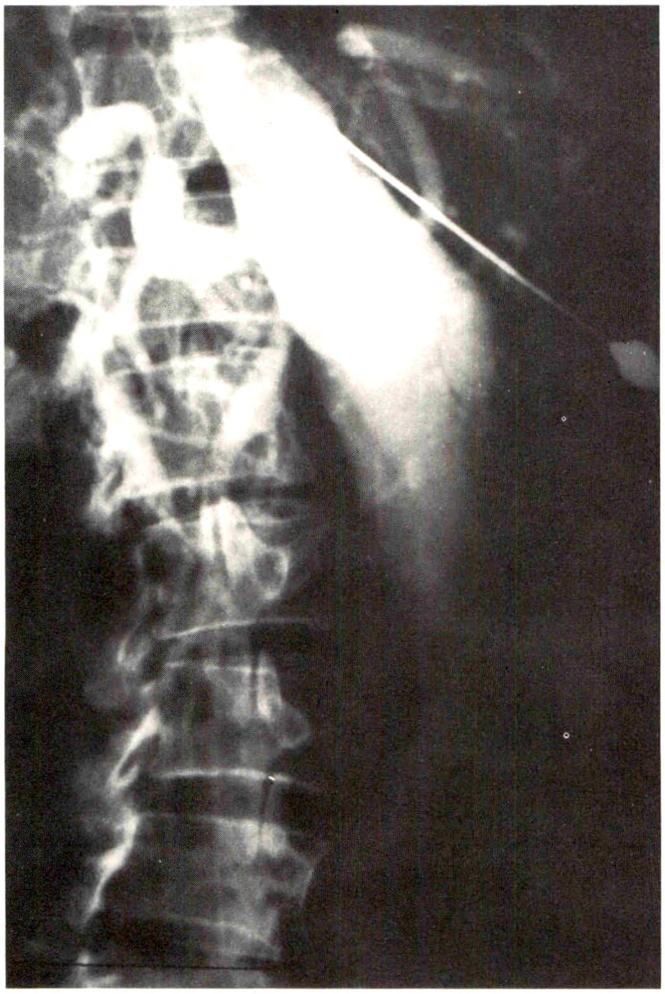


FIG. 1. Translumbar aortogram shows aneurysmal degeneration of hepatic artery and abdominal aorta.

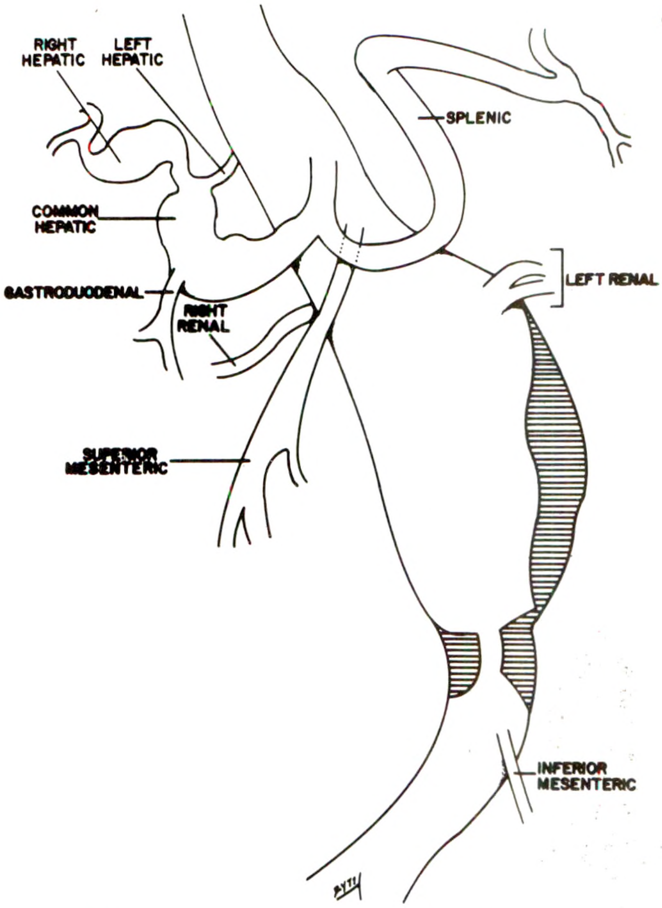


FIG. 1A. Line drawing of translumbar arteriogram.

An arteriogram obtained 2 weeks following operation is shown in Figure 2. The distal right hepatic artery is not visualized in an early phase but is well seen in a later sequential film, indicating probable occlusion of the spleno right hepatic artery anastomosis with reconstitution via collateral flow.

Discussion

The occurrence of multiple nonatheromatous aneurysms in this relatively young patient raises the question of etiology.

The past history of tuberculosis suggests the possibility of mycotic aneurysm formation, but the duration of history and absence of other signs of persistent infection seems to exclude this.

The atypical aortic aneurysm could be due to idiopathic medial aortopathy and arteriopathy, a pathologic entity described by Marquis *et al.*[5] which attempts to bring together under one heading several disease states characterized by medial degeneration of the aorta and its proximal branches. Peripheral visceral aneurysms are not included in their description, however, and we have no pathologic evidence to support the possibility

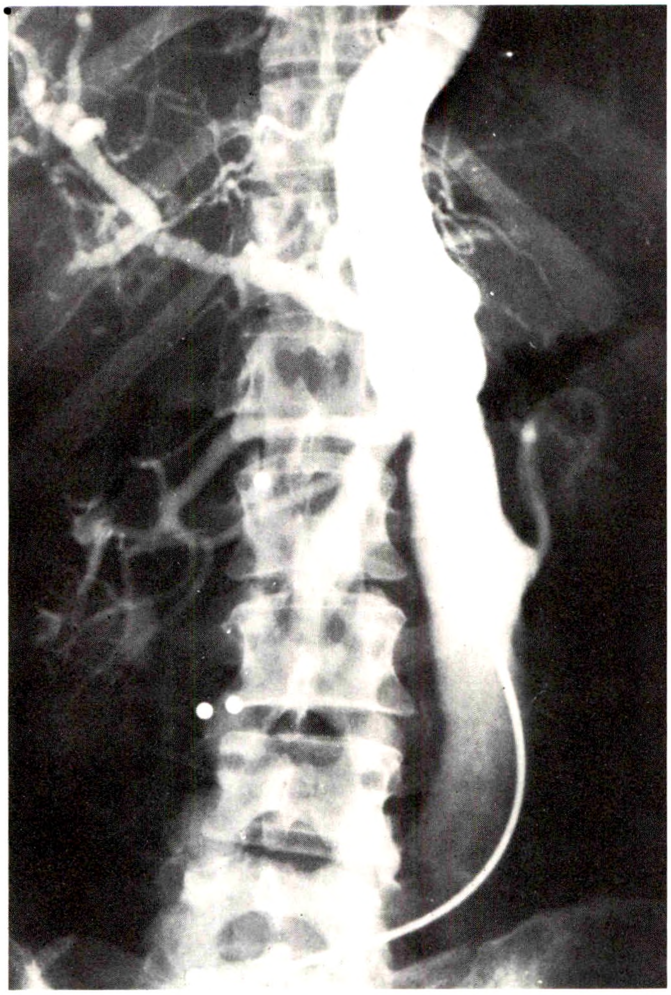


Fig. 2. Postoperative arteriogram shows probable occlusion of spleno-right hepatic artery anastomosis.

that our patient represents another variant of this condition.

Multiple visceral aneurysms may occur in polyarteritis nodosa. Characteristically they involve the kidney, but multiple aneurysms within the liver, spleen, and along the peripheral branches of the superior mesenteric artery may occur.[1] The latter finding is suggested by the postoperative arteriogram in our patient. Usually, only small and medium sized arteries are involved in polyarteritis nodosa, however, tending to exclude this diagnosis in our patient.

The cystadenoma of the pancreas, while perhaps not etiologically related to the aneurysm formation, is an interesting coincidental finding, and is reminiscent of a case of renal and hepatic cysts associated with multiple aneurysms in the Ehlers-Danlos Syndrome.[4] Arterial abnormalities may be the most prominent manifestation of the Ehlers-Danlos Syndrome in some patients with that disease[4] and the occurrence of multiple nonatheromatous aneurysms raises this diagnostic possibility. The absence of histologic connective tissue abnormalities does not exclude this diagnosis.

Our patient does not clearly fit into any of the above disease classifications. A systemic condition or basic connective tissue defect involving the arteries seems likely. Pathologic examination of the arterial segments in the spleen and pancreas revealed no abnormalities to explain the pathophysiologic process in our patient. It is regrettable that we did not consider biopsy of the aorta at the time of operation.

The technical aspects of this case are of some interest. Hepatic aneurysm exclusion with splenic artery bypass has been used successfully by McCorriston *et al.*[6] and subsequently by others.[3] In previous cases the splenohepatic anastomosis was proximal to the hepatic artery bifurcation. We believe our case represents the first anastomosis of the splenic artery separately to the right and left branches of the hepatic artery. This, of course, was necessitated by the findings in our case.

Other technical principles employed in managing this

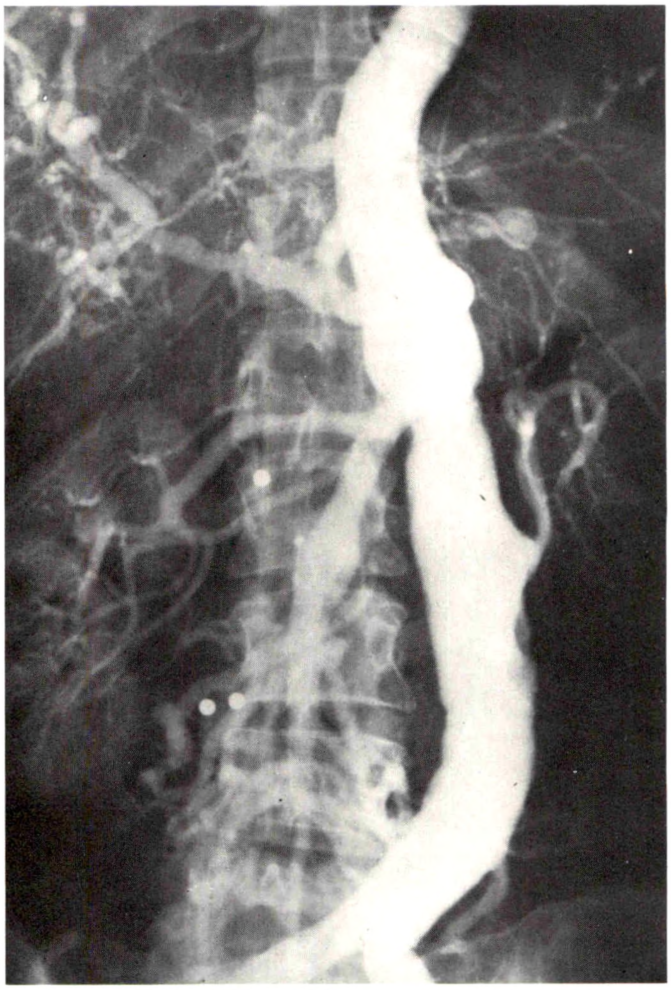


Fig. 2A. Later sequential film of postoperative arteriogram shows reconstitution of distal right hepatic artery by collateral flow.

patient included division of the left renal vein to facilitate exposure, with subsequent reanastomosis;[8] cuff reinforcement of high aortic anastomosis, including the origins of the superior mesenteric and right renal arteries;[7] and reimplantation of left renal artery into aortic graft.[2] None of these technics are original or difficult, but to use all of them in one operation is unusual; to employ them in combination with resection of a pancreatic tumor is, we feel, somewhat unique.

Summary

The case of a relatively young woman with high abdominal aortic aneurysm associated with hepatic artery aneurysm and cystadenoma of the pancreas is reported. The operative management which resulted in a successful early outcome is described. Some questions are raised as to possible etiology of this interesting and unusual association of clinical conditions.

Addendum

The patient is alive and well 15 months following operation.

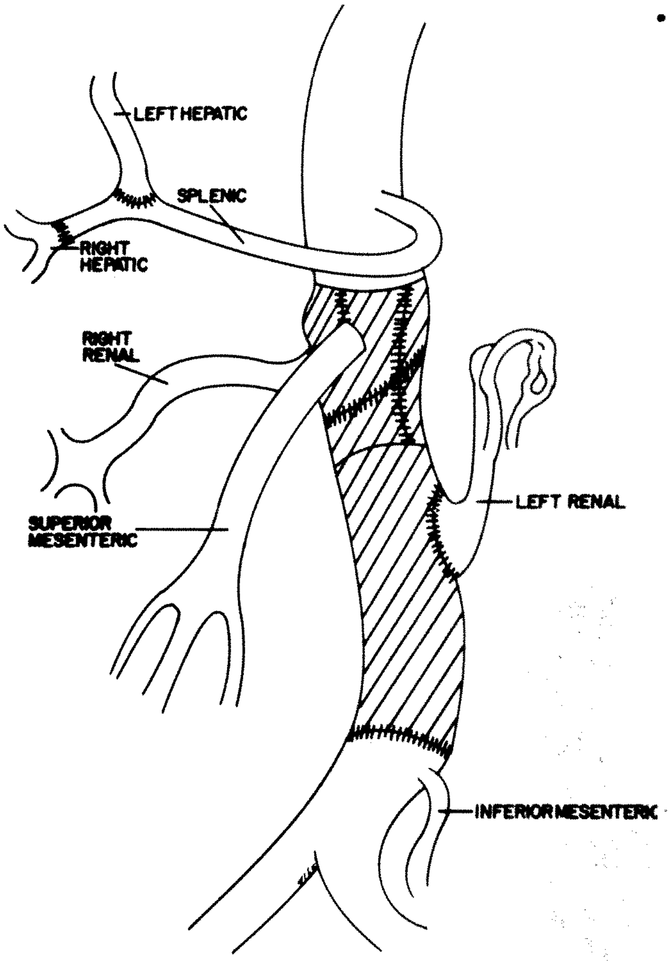


FIG. 2B. Line drawing depicts completed operation.

References

1. Bron, K. M., Strott, C. A., Shapiro, A. P.: The Diagnostic Value of Angiographic Observations in Polyarteritis Nodosa: A Case of Multiple Aneurysms in the Visceral Organs. Arch. Int. Med., **116**:450, 1965.
2. Carrel, A.: The Surgery of Blood Vessels, etc. Johns Hopkins Hosp. Bull. No. 190, January 1907.
3. Gardner, W. J., Howe, R. F., Olsen, D. D.: Aneurysm of the Hepatic Artery Treated by Exclusion with Splenic Artery Bypass. Am. J. Surg., **118**:947, 1969.
4. Imahori, S., Brannerman, R. M., Graf, C. J., Brennan, J. C.: Ehlers-Danlos Syndrome with Multiple Arterial Lesions. Am. J. Med., **47**:967, 1969.
5. Marquis, Y., Richardson, J. B., Ritchie, A. C., Wigle, E. D.: Idiopathic Medial Aortopathy and Arteriopathy. Am. J. Med., **44**:929, 1968.
6. McCorriston, J. R., Allen, G. E., Crowell, D. E.: Splenohepatic Arterial Anastomosis for Aneurysm of the Hepatic Artery. Surgery, **47**:636, 1960.
7. Robicsek, F., Mullen, D. C., Daugherty, H. K.: Aortic Aneurysms Involving the Origin of the Renal Arteries: A Simple Solution to a Complicated Problem. Surgery, **70**:425, 1971.
8. Szilagyi, D. E., Smith, R. F., Elliott, J. P.: Temporary Transection of the Left Renal Vein: A Technical Aid in Aortic Surgery. Surgery, **65**:32, 1969.

Effect of Truncal, Selective and Highly Selective Vagotomy on Gastric Emptying and Intestinal Transit of a Food-Barium Meal in Man

ALAN R. WILKINSON, MB, ChB, FRCS, DAVID JOHNSTON, FRCS (ED. & GLASG.)

From the University Department of Surgery, The General Infirmary, Leeds 1, Britain

BOTH TRUNCAL VAGOTOMY[10] and bilateral selective vagotomy,[12,18] when used alone, have produced gastric stasis in man.[4,11] This is not surprising, since both procedures effect the entire stomach,[25] including the antrum. In consequence, the addition of a drainage procedure is necessary. However, the combination of complete gastric vagotomy with pyloroplasty or gastrojejunostomy leads to abnormally-rapid gastric emptying,[6,7,20,22,25] which in turn may produce side-effects such as dumping and diarrhea.[17,22,23]

Highly selective vagotomy (HSV) is confined to the parietal cell mass.[1,19] The antrum remains innervated, eliminating the addition of a drainage procedure[1,19] and side-effects are much reduced.[16,20] This study compares gastric emptying in patients after HSV with gastric emptying in patients before operation and in patients after truncal or selective vagotomy with pyloroplasty. The main questions to be answered were: first, was there evidence of gastric stasis after HSV, and, second, was the pattern of gastric emptying and small bowel transit closer to the preoperative pattern after HSV than after vagotomy with pyloroplasty?

Method

Patients

Thirteen patients with duodenal ulceration (DU), without clinical or radiologic signs of pyloric stenosis, were studied before operation. Patients who were studied after vagotomy were in good health (nearly all in Visick I and II[13]), 1 to 3 years after operation, and in each the vagotomy had been complete in insulin testing[15] in the early postoperative period.

All the patients were men, with the exception of two women in the selective vagotomy group and one woman in the HSV group. Twelve patients had undergone truncal vagotomy and pyloroplasty (TV + P); 10 had bilateral selective vagotomy and pyloroplasty (SV + P), and 14 underwent highly selective vagotomy without drainage (HSV). The pyloroplasty was of the Heinecke-Miculicz type in each case. The mean (±1 SE) ages of the patients were 45.1 ± 3.7 (DU), 49.8 ± 3.5 (TV + P), 44.8 ± 2.4 (SV + P), and 44.5 ± 2.5 years (HSV). Mean weights were, respectively, 67.3 ± 2.3 Kg. (DU), 68.2 ± 1.8 (TV + P), 62.9 ± 2.7 (SV + P) and 68.3 ± 1.9 Kg. (HSV).

Meal

The meal consisted of two slices of toast, one ounce (28 Gm.) of butter, two scrambled eggs, 170 ml. of tea with milk and one teaspoonful of sugar, 30 ml. of 'Raybar' and 30 ml. of water. These ingredients were homogenized in a blender for 10 minutes. The resulting meal was semi-fluid in consistency and tasted surprisingly pleasant, like a rather chalky cake-mix. It was served warm, and eaten with a spoon because it was too thick to drink.

Procedure

The test began at 6 p.m., after the patient had fasted from lunchtime, about 1 p.m. First, a plain X-ray film of the abdomen was taken. Then the patient sat upright in a chair, and ate the meal in the course of 5 to 10

Submitted for publication January 16, 1973.

Request reprints: Mr. David Johnston, The University Department of Surgery, The General Infirmary, Leeds 1, Britain.

minutes. Further abdominal radiographs were taken, 15, 30, 45, 60, 90, 120 and 150 minutes from the start of the meal, with the patient lying prone on the X-ray table. In the intervals between exposures, he sat in a chair, or strolled about the X-ray Department.

Assessment

The films were assessed by an experienced radiologist, who was unaware of the group to which the patient belonged. He was asked to answer three questions: (1) Which was the first film which showed the start of gastric emptying (*i.e.* the presence of barium in the duodenum or beyond). (2) When was the stomach completely empty? (apart perhaps from the merest traces of barium clinging to the gastric mucosa). (3) When did the head of the meal reach the colon?

Statistics

Differences between groups were analyzed by means of the Mann-Whitney test[21] for non-parametric data.

Results

Time Interval before the Start of Gastric Emptying.

Gastric emptying had begun by the time the 15-minute film was exposed in all the patients who had undergone TV + P or SV + P, but in only 10 of the 13 preoperative DU patients and 12 of the 14 patients after HSV (Fig. 1). These differences are not statistically significant. By 30 minutes, gastric emptying had begun in all patients.

Time Required for Stomach to Empty Completely.

Gastric emptying was significantly faster in patients who had undergone TV + P ($p < 0.002$) or SV + P ($p < 0.002$) than in preoperative DU patients. Gastric emptying was also significantly faster after TV + P than after HSV ($p < 0.002$), and significantly faster after SV + P than after HSV ($p < 0.01$). There was no significant difference between the rates of gastric emptying in DU and HSV patients (Fig. 2). For example, 90 minutes after the meal, the stomach was completely empty in none of the 13 DU patients, nine of 12 patients after TV + P, five of ten patients after SV + P, and two of 14 patients after HSV.

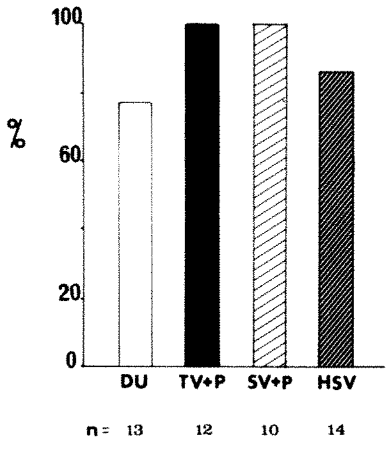


FIG. 1. In most patients, barium was visible in the duodenum or beyond at 15 minutes. The start of gastric emptying is slightly faster in patients after TV + P and SV + P than in preoperative DU patients or patients after HSV. By 30 minutes, gastric emptying had begun in all patients.

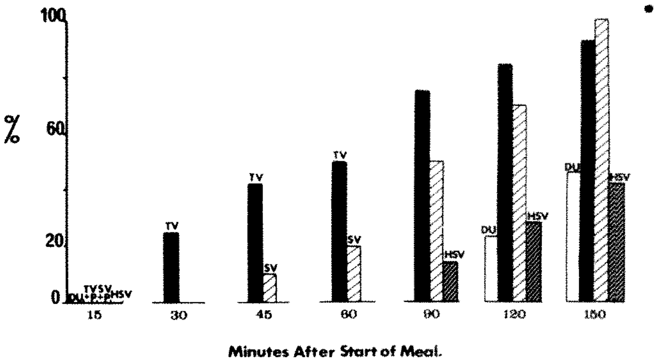


FIG. 2. Patients after truncal vagotomy and pyloroplasty (TV) had significantly faster ($p < 0.002$) gastric emptying than had either patients with duodenal ulcer before operation (DU) or patients who had undergone highly selective vagotomy (HSV). Though gastric emptying in the selective vagotomy–pyloroplasty group (SV) was slightly slower than in patients after TV + P, it was significantly faster than in DU patients ($p < 0.002$) or HSV patients ($p < 0.01$). The pattern of gastric emptying after HSV was similar to that observed in preoperative DU patients.

Time Required for the Head of the Meal to Reach the Cecum.

Small bowel transit, as judged by the time required for the head of the meal to reach the colon, was significantly faster in patients after TV + P ($p < 0.002$) and SV + P ($p < 0.002$) than in preoperative DU patients (Fig. 3). Small-bowel transit was also slightly faster in HSV patients than in preoperative DU pa-

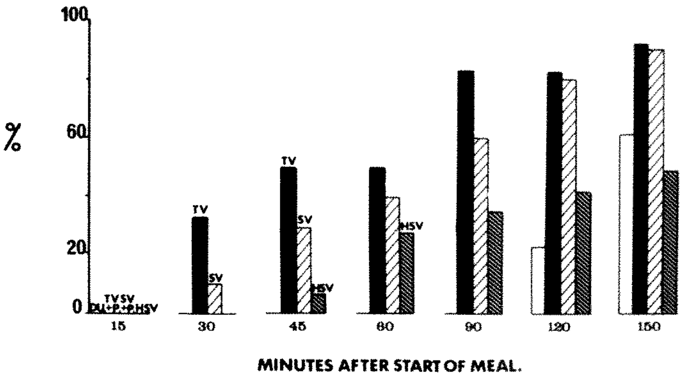


FIG. 3. Transit of the head of the meal through stomach and small intestine was significantly faster after truncal vagotomy–pyloroplasty (TV) than before operation (DU: $p < 0.002$), or than after highly selective vagotomy (HSV: $p < 0.05$). Similarly, gastro-intestinal transit was significantly faster in the selective vagotomy–pyloroplasty group (SV) than in preoperative DU patients ($p < 0.002$). The HSV and DU groups of patients did not differ significantly.

tients, but the difference was not statistically significant. Barium reached the colon significantly faster after TV + P than after HSV ($p < 0.05$), but the difference between the SV + P and HSV groups was not very significant ($p < 0.1$). For example, 45 minutes postcibum the head of the meal had reached the colon in none of the preoperative DU patients, six of 12 TV + P patients, three of 10 SV + P patients and one of 14 HSV patients. Ninety minutes after the meal, barium had reached the colon in none of the DU patients, 10 of 12 TV + P patients, six of 10 SV + P patients and five of 14 HSV patients.

Discussion

A radiologic method such as this is a relatively crude way of investigating gastric emptying. It is capable only of demonstrating the existence of large differences between groups of subjects. One cannot, for example, state that the stomach is 35% empty or 80% empty. However, certain definite statements can be made. One can say that gastric emptying has started or that it has not; that the stomach is completely empty or that it is not; and that the head of the meal has reached the colon or that it has not. Emptying of the thick food-barium paste is likely to give a better estimate of the emptying of a normal meal than would barium alone.

It is assumed, on the basis of previous work by others,[14] that gastric emptying is normal, or at least not slower than normal, in patients with duodenal ulcer who do not have clinically-manifest pyloric stenosis.

The results which we have obtained are in accord with those of previous workers[6, 22, 23, 26] who found that gastric emptying of fluids was significantly faster after truncal or selective vagotomy with a drainage procedure than in patients with duodenal ulcer before operation. They are also in agreement with reports that gastric emptying of fluids,[5] and of food-and-barium,[24] is not delayed after HSV. Our results are not in agreement with the report by Buckler[2] that gastric emptying was delayed after truncal vagotomy and pyloroplasty, nor with that of Cowley *et al.*[8] who found that gastric emptying was normal after truncal vagotomy and pyloroplasty. Buckler[2] and Cowley *et al.*[8] used a test meal of solid food, which may explain why gastric emptying in their patients was slower than in our patients after TV + P or SV + P, in whom the test meal was semi-fluid. The posture adopted by the patients during the test may also provide an explanation for the differing results, because Cowley's *et al.*[8] patients were kept in a recumbent position throughout the test, whereas our patients sat in a chair or walked about except when radiographs were being taken. According to the work of McKelvey *et al.*,[22,23] posture does not exert an important influence on gastric emptying in the intact individual, but after vagotomy with a drainage procedure it assumes great importance. Gastric emptying is retarded if the patient lies supine and is rotated towards the left, whereas emptying is precipitate if the patient assumes the upright posture. These findings of McKelvey *et al.*[22,23] apply only to fluids, but they are probably relevant to the emptying of normal meals. For example, a normal dinner consists of fluids (aperitif, soup) followed by solids and semi-solids (meat, gravy and potatoes), followed by solids with hypertonic liquid (fruit salad with syrup and ice-cream), followed by more fluids (coffee). The conclusions of Cowley *et al.*[8] that gastric emptying is within the normal range after TV + P are also difficult to accept because it is known that 10 to 30 per cent of patients experience early dumping in the first year after TV + P or SV + P,[16] which strongly suggests that their gastric emptying is abnormally rapid. Finally, after the demonstration by Code *et al.*[3] that the pylorus and the terminal antrum discriminate between solids and liquids, holding back solids and retropelling them into the body of the stomach while liquids are allowed to pass, it seems inconceivable that gastric emptying of solids should be normal when the pylorus has been destroyed by pyloroplasty or bypassed by gastrojejunostomy. Indeed, it was subsequently shown by Dozois *et al.*[9] that after the terminal antrum is excised, solid spheres empty more rapidly from the stomach of dogs.

Summary

Gastric emptying of a food-barium meal was measured radiographically in patients with duodenal ulcer without pyloric stenosis before operation, and in well-matched groups of patients who were in good health more than 1 year after highly selective vagotomy, truncal vagotomy and pyloroplasty and selective vagotomy and pyloroplasty. In each patient, the vagotomy was complete on insulin testing in the early postoperative period. The meal was palatable, and semi-solid in consistency. The patients were allowed to sit in a chair or to walk about in the intervals between X-rays.

The meal began to leave the stomach slightly earlier, but not significantly, in patients after truncal and selective vagotomy with pyloroplasty than in preoperative patients or patients after highly selective vagotomy.

The stomach was completely empty significantly sooner in patients who had undergone truncal and selective vagotomy with pyloroplasty than in duodenal ulcer patients or in patients after highly selective vagotomy.

The head of the meal reached the colon significantly sooner in patients after truncal and selective vagotomy with pyloroplasty than in preoperative duodenal ulcer patients. Thus, gastrointestinal transit was significantly

faster in patients who had undergone truncal or selective vagotomy with pyloroplasty than in patients with duodenal ulcer before operation. In patients after HSV, small-bowel transit was slightly faster than in duodenal ulcer patients, but was much less rapid than in patients after truncal or selective vagotomy with pyloroplasty.

These findings indicate that gastric emptying and small-bowel transit times are closer to normal in patients who have undergone HSV than in patients who have undergone truncal or selective vagotomy with pyloroplasty. On the other hand, there was no evidence of delayed gastric emptying after highly selective vagotomy.

Acknowledgments

We thank Professor J. C. Goligher for his interest and support of this work. We are indebted to our colleagues in the Department of Radiology, Miss Anne Hawkswell and Dr. G. J. S. Parkin for valuable assistance. We are grateful to Mr. F. T. de Dombal for help with the statistical analysis.

References

1. Amdrup, E. and Jensen, H-E.: Selective Vagotomy of the Parietal Cell Mass Preserving Innervation of the Undrained Antrum. Gastroenterology, **59**:522, 1970.
2. Buckler, K. G.: Effects of Gastric Surgery upon Gastric Emptying in Cases of Peptic Ulceration. Gut, **8**:137, 1967.
3. Carlson, H. C., Code, C. F. and Nelson, R. A.: Motor Action of the Canine Gastro-duodenal Junction: a Cineradiographic Pressure and Electric Study. Am. J. Dig. Dis., **11**:155, 1966.
4. Clarke, R. J., McFarland, J. B. and Williams, J. A.: Gastric Stasis and Gastric Ulcer after Selective Vagotomy without a Drainage Procedure. Br. Med. J., **1**:538, 1972.
5. Clarke, R. J. and Williams, J. A.: The Effect of Antral Denervation and Pyloroplasty on Gastric Emptying and Dumping." Paper to Surgical Research Society, Liverpool, July 1972.
6. Cobb, J. S., Bank, S., Marks, I. N. and Louw, J. T.: Gastric Emptying after Vagotomy and Pyloroplasty. Relation to Some Post-operative Sequelae. Am. J. Dig. Dis., **16**:207, 1971.
7. Colmer, M. R., Davies, W. T., Owen, G. M. and Shields, R.: 'Dumping' after Vagotomy and Pyloroplasty. Br. J. Surg., **56**:702, 1969.
8. Cowley, D. J., Vernon, P., Jones, T., Glass, H. I. and Cox, A. G.: Gastric Emptying of Solid Meals after Truncal Vagotomy and Pyloroplasty in human subjects. Gut, **13**:176, 1972.
9. Dozois, R. R., Kelly, K. A. and Code, C. F.: Effect of Distal Antrectomy on Gastric Emptying of Liquids and Solids. Gastroenterology, **61**:675, 1971.
10. Dragstedt, L. R. and Owens, F. M., Jr.: Supra-diaphragmatic Section of the Vagus Nerves in the Treatment of Duodenal Ulcer. Proc. Soc. Exp. Biol. Med., **53**:152, 1943.
11. Dragstedt, L. R. and Woodward, E. R.: Appraisal of Vagotomy for Peptic Ulcer after Seven Years. JAMA, **145**:795, 1951.
12. Franksson, C.: Selective Abdominal Vagotomy. Acta. Chir. Scand., **96**:409, 1948.
13. Goligher, J. C., Pulvertaft, C. N., de Dombal, F. T., Clark, C. G., Conyers, J. H., Duthie, H. L., Feather, D. B., Latchmore, A. J. C., Harrop-Shoesmith, J., Smiddy, F. G., and Willson-Pepper, J.: Five- to Eight-year Results of Leeds/York Controlled Trial of Elective Surgery for Duodenal Ulcer. Br. Med. J., **2**:781, 1968.
14. Griffith, G. H., Owen, G. M., Campbell, H. and Shields, R.: Gastric Emptying in Health and in Gastro-duodenal Disease. Gastroenterology, **54**:1, 1968.
15. Hollander, F.: Laboratory Procedures in the Study of Vagotomy (with particular reference to the insulin test). Gastroenterology, **11**:419, 1948.
16. Humphrey, C. S., Johnston, D., Pulvertaft, C. N., Walker, B. E. and Goligher, J. C.: The Incidence of Dumping after Truncal, Selective and Highly Selective Vagotomy in Man. Br. Med. J., **3**:785, 1972.
17. Humphrey, C. S. and Wilkinson, A. R.: The Importance of Preserving the Pylorus in Surgery for Duodenal Ulcer. Br. J. Surg., **59**:779, 1972.
18. Jackson, R. G.: Anatomic Study of the Vagus Nerves, with a Technic of Transabdominal Selective Gastric Vague Resection. Arch. Surg. (Chicago), **57**:333, 1948.
19. Johnston, D. and Wilkinson, A. R.: Highly Selective Vagotomy without a Drainage Procedure in the Treatment of Duodenal Ulcer. Br. J. Surg., **57**:289, 1970.
20. Johnston, D., Humphrey, C. S., Pulvertaft, C. N., Walker, B. E. and Goligher, J. C.: Vagotomy without Diarrhoea. Br. Med. J., **3**:788, 1972.
21. Mann, H. B. and Whitney, D. R.: On a Test of Whether One of Two Random Variables is Statistically Larger Than the Other. Ann. Math. Statist., **18**:50, 1947.
22. McKelvey, S. T. D., Connell, A. M. and Kennedy, T. L.: Gastric Emptying and Transit Time as Factors in Post-vagotomy Diarrhoea (Abstract) Gut, **10**:1047, 1969.
23. McKelvey, S. T. D.: Gastric Incontinence and Post-vagotomy Diarrhoea. Br. J. Surg., **57**:741, 1970.
24. Pedersen, G. and Amdrup, E.: The Gastrointestinal Passage of a Physiological Contrast Medium in Duodenal Ulcer Patients before and after Vagotomy of the Parietal Cell Mass with Preserved Antral Innervation or a Selective Gastric Vagotomy with Finney Pyloroplasty. In Advance Abstracts, 4th World Congress of Gastroenterology, p. 433, Daniel Gastroent. Ass., Copenhagen, 1970.
25. Stavney, L. S., Kato, T., Griffith, C. S., Nyhus, L. M. and Harkins, H. N.: A Physiologic Study of Motility Changes Following Selective Gastric Vagotomy. J. Surg. Res., **3**: 390, 1963.
26. Waddell, W. R. and Wang, C. C.: Effect of Vagotomy on Gastric Evacuation of High-fat Meals. J. Appl. Physiol., **5**:705, 1952.

Congenital Obstruction of the Pancreatic Duct at the Duodenum:

A Report of Two Cases in Adulthood

THOMAS TAYLOR WHITE, HELGE KAVLIE

From the Departments of Surgery, University of Washington and Swedish Hospitals, Seattle, Washington

ACUTE ATTACKS of pancreatitis have been reported to relate to gallstone disease, alcoholism, operative and external trauma, and many other metabolic and infectious processes, however, there have been infrequent reports of childhood pancreatitis with a dilated duct which appeared to be secondary to a congenital narrowing of the pancreatic duct at/or near the sphincter of Oddi.[2,3,5,6,8,9,10] The two patients presented here both had histories of recurrent episodes of abdominal pain first appearing in childhood. Only many years later, in adulthood, were they found to have recurrent, acute pancreatitis, for which they were treated surgically. Neither patient had gallstones or drank alcohol excessively. In both patients there was an almost complete stricture of the duct of Wirsung at the duodenum with a grossly dilated pancreatic duct behind the stricture.

While congenital stricture of the papilla has been reported to be a cause of recurrent biliary symptoms due to biliary hypertension, we have not heard before of a stricture sufficient to produce marked dilatation of the pancreatic ductal system behind it. Our reason here is to report our two cases of marked dilatation of the pancreatic duct behind such a narrowing.

Case Reports

Case 1. The first patient, a 22-year-old woman, Mrs. J. V. (University Hospital 13–36–19) was admitted to another hospital on July 11, 1969 with a chief complaint of abdominal pain. She had had recurrent episodes of abdominal pain prior to this time, with no definite diagnosis. The hospital course was one of continued abdominal pain with amylase levels ranging from 3 to 15 times normal. Because attempts to treat the patient medically had failed she was transferred to University Hospital for further evaluation. On admission July 23, 1969 she stated that there had been prior episodes of similar pain, precipitated by eating, which were aborted by refraining from eating solids. She had had episodes of abdominal pain since the age of 4, and had been admitted to the Children's Orthopedic Hospital in Seattle at the ages of 7 and 11 with undiagnosed abdominal pain. At the age of 16 she was admitted to the Doctors Hospital in Seattle with a sudden epigastric pain which was believed to be caused by pancreatitis but there was no elevation of amylase. She was admitted twice to a hospital in California with severe abdominal pains. On neither of these occasions did she have elevations of amylase. She had had three upper gastrointestinal X-ray studies, five of the gallbladder and three barium enemas X-ray all of which were reported to be normal. Her parents on both sides of the family had strong histories of gallstones.

The physical examination at University Hospital was essentially negative except that she had lesions on both lower legs, one of which, on biopsy, showed fat necrosis. Further attempts at medical therapy were unsuccessful. Her blood amylase level remained at approximately eight times greater than normal. At surgical exploration July 31, 1969 she had a tremendous amount of inflammation and fat necroses around the pancreas. A 2 cm. pancreatic duct could be readily palpated along the anterior surface of the pancreas. The gallbladder was very much inflamed, yet the common bile duct was of normal diameter. Because, we initially thought that the entire process might be secondary to biliary disease, first, we performed a cholecystectomy and manometric cholangiograms. She had elevated intrabiliary pressures, approximately 26 cm. of water (normal 0–16). For this reason, the duodenum was opened and a 2 cm. sphincteroplasty was carried out. Pancreatograms showed the great dilatation of the pancreatic ductal system (Fig. 1). An attempt to perform a sphincteroplasty up to the point of obstruction just to the right of the spine was unsuccessful. For this reason the anterior wall of the pancreas was

---

Submitted for publication July 10, 1972.

This work was supported in part by NIH Grant AM 11358.

Request reprints: Thomas Taylor White, M.D., Department of Surgery RF 25, University of Washington, Seattle, Washington 98195.

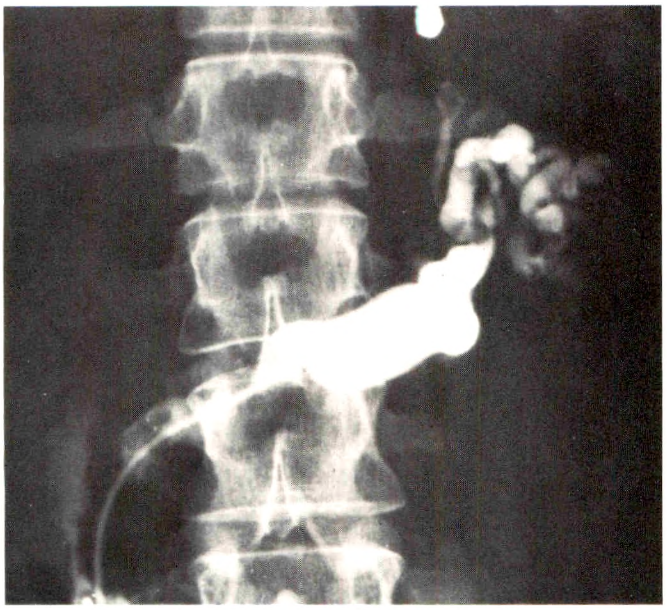


FIG. 1. Pancreatogram shows the great dilatation of the pancreatic ductal system.

incised. A probe which was passed into the duct entered the duodenum about 2 cm. above the entrance of the bile duct at the papilla of Santorini. Since it was clear that the dilated duct stopped immediately against the duodenum, we also performed a 15 mm. sphincteroplasty on this papilla. The biopsy specimen of this papilla showed chronic inflammation. We felt that the pancreas could be drained adequately by this procedure alone. The patient appeared to do very well and was discharged on the sixteenth postoperative day.

Unfortunately, she continued to complain of nausea and gas pains in both flanks. When she was readmitted on October 6, 1969, she was febrile, tender in the left upper quadrant, and appeared to have developed an intra-abdominal abscess. At a second operation on October 19, 1969, the patient was noted to have a pancreatic abscess containing coagulase positive staphylococci in the left upper quadrant which was adherent to the posterior aspect of the stomach, the spleen, and the mesocolon. The spleen and the entire inflammatory mass of pancreas were resected over to the aorta. The pancreatic duct was then opened longitudinally 4 cm. and anastomosed by a side-to-side anastomosis to a Roux-Y loop of the jejunum. The patient tolerated this procedure well and was discharged from hospital again 2 weeks later. The patient had a pancreatic fistula which closed spontaneously 3 months later. Following this, she had a number of suture sinuses. She is completely asymptomatic in April 1973.

Case 2. Mrs. E.B. (Swedish Hospital 094-16-1673; University Hospital 00-18-78) had history of epigastric pain dating to 4 or 5 years af age. She did not relate the epigastric distress to eating until the age of 16. At 42 years of age her problem was diagnosed to be a very mild ulcerative colitis. She continued to have mild attacks of abdominal pain and diarrhea until pancreatic calcifications were noted in 1968 at 50 years of age. At that time she began to develop intermittent mild jaundice. On physical examination a tender epigastric mass was noted which was thought to be caused by pancreatitis. She was admitted on two further occasions to Swedish Hospital for possible acute attacks of pancreatitis. During this period it was found that both her father and her paternal grandmother had had similar symptoms and signs and calcification since childhood but that no operative or autopsy diagnosis had been made to confirm the diagnosis of a similar problem.

Finally, the disease process became so acute that a laparotomy was performed at the Swedish Hospital on February 19, 1970, when she was 52 years old. At that time the pancreas was enormously inflamed with fat necrosis throughout. The pancreatic duct was dilated to approximately 2 cm. throughout its length. There were numerous stones within the pancreatic duct and the branches thereof. There was an enormous amount of edema of the tissues around the portal triad with an enlarged gallbladder. After the gastrocolic ligament was opened turbid fluid could be aspirated from the pancreas. This was replaced with 50% Hypaque and X-rays were taken which showed an enormous dilatation of the whole ductal system (Fig. 2). The duct was then opened with cautery and scissors throughout its length. A Roux-Y loop was constructed and sutured for approximately 18 cm. along the anterior surface of the pancreas. At this time the inflammatory process in the left upper quadrant was so great that it was decided to do nothing to that area. The patient did reasonably well for several weeks until on April 3, 1970, she developed a severe gastrointestinal hemorrhage which appeared to be caused by a duodenal ulcer. After two transfusions there was significant improvement. The patient appeared to be well for several months and then

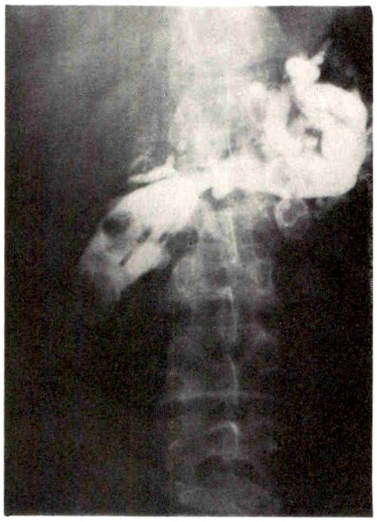


FIG. 2. Enormous dilatation of the entire ductal system.

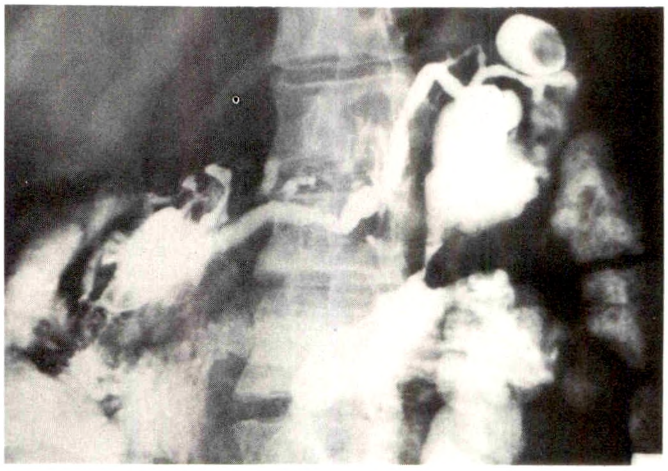


FIG. 3. Fistulous tract extends from the abscess cavity through and inward to connect with the pancreatic ductal system.

Suddenly she developed a feeling of fullness in the upper abdomen. X-rays showed that the stomach was pushed anteriorly and to the right. On October 21, 1970 an 18 cm. mass in the left upper quadrant was drained of extremely foul smelling purulent material containing anaerobic streptococcus. The cystic area was first aspirated with a needle then with a trocar of about 450 cc. of purulent material. A large pezzar catheter was brought out through the abdominal wall of the surface and the cyst sutured to the abdominal wall. The patient improved at first and then again developed chills and fever. X-rays through the catheter showed a fistulous tract extending from the abscess cavity through and on inward to connect with the pancreatic ductal system (Fig. 3). Because of the severe inflammatory nature of the problem, first she was treated with antibiotics. Finally, on November 17, 1970, the fistulous tract from the abdominal wall was dissected down to the tail of the pancreas and the spleen and pancreas were resected to about 2 cm. from the aorta approximately flush with the left end of the previously constructed pancreaticojejunostomy. The left upper quadrant was then irrigated with 500 ml. saline containing 1 gm of Keflin. Three large split drains were left in this area.

She then developed a sinus tract from the upper quadrant of the abdomen which was very resistant to treatment and required redrainage of the abscess and excision of sinus tracts in June, October and November, 1971. In April 1973 she is asymptomatic.

Discussion

In a recent article by Boyden *et al.*[1] on congenital duodenal obstruction, a number of significant new details were added. They point out that "a state of temporary interruption of the duodenal lumen passes progressively downward through the entire duodenum between the thirtieth and fiftieth days of gestation. The epithelium, starting to grow while surrounding mesenchymal walls are still narrow, fills or partially fills the lumen with its proliferating cells. Then the central core of cells is progressively *loosened* by vacuoles arising between the core and the future definitive epithelial wall. Coalescence of vacuoles at first produces two parallel channels. Into each of these the bile and accessory pancreatic ducts acquire openings. The presence of these four orifices mechanically delays the formation of the main channel, producing a traffic jam. If a given segment remains solidly epithelial for a critical period, it will be resorbed and replaced by mesenchyma and its derivative tissues. Partial blocking of channels may result in stenosis instead of atresia," either of the duodenum, the bile ducts, or the pancreatic ducts. In any case the process appears to be secondary in these instances either to the process within the duodenum itself, or to noncompletion of vacuolization of the pancreatic duct as it buds from the ventral pancreas.

Conversely hypertrophy of the sphincter of Oddi may have been the original cause of difficulty in these two patients.[4,7] The close application of the distorted distal duct to the duodenum makes this possible although not clear cut.

As far as the diagnosis is concerned it is one which will be made largely by accident, when the patient develops an attack of acute pancreatitis, or as in the second patient, when the patient develops calcification of the pancreas. The clinical treatment of these patients is complicated because their pancreases are functional rather than fibrotic as in the usual case of chronic pancreatitis, with a dilated duct and leak pancreatic juice into the operative area during the postoperative period, which can cause cyst formation, abscesses, or fistulas. Our experience and that of others in the treatment of patients with a normally functioning islet cell tumor has been fraught with a nearly 50% rate of pancreatic cysts, fistulas, and abscesses secondary to infection of pancreatic juice which has spilled into the surrounding tissues. We have not, as yet, found a method of preventing this leakage and abscess formation. It probably would have been better in each of these two cases to resect the spleen and left half of the pancreas early in the course of the disease, but this might have produced excessive hemorrhage and, indeed, death.

Summary

Congenital obstruction of the pancreatic duct at the duodenum was found in two adults, 22 and 52 years old. Both had been complaining of intermittent abdominal pain since early childhood. One had a parent and grandparent in whom calcification occurred after a similar course. In neither instance was the cause of pain discovered until the patients developed an attack of acute pancreatitis. Both were treated by resection of the tail of the pancreas and pancreaticojejuostomy with subsidence of symptoms and signs.

References

1. Boyden, E. A., Cope, J. G. and Bill, A. H., Jr.: Anatomy and Embryology of Congenital Intrinsic Obstruction of the Duodenum. Am. J. Surg., **114**:190, 1967.
2. Comfort, M. W. and Steinberg, A. G.: Pedigree of a Family with Heredity Chronic Relapsing Pancreatitis. Gastroenterology, **21**:54, 1952.
3. Dean, R. H., Scott, H. W., Jr. and Law, D. H., IV.: Chronic Relapsing Pancreatitis in Childhood: Case Report and Review of the Literature. Ann. Surg., **173**:443, 1971.
4. Hermann, R. E. and Davis, J. H.: The Role of Incomplete Pancreatic Duct Obstruction in the Etiology of Pancreatitis. Surgery, **48**:318, 1960.
5. Ingomar, C. J. and Teisler, E.: A Case of Chronic Pancreatitis in Early Childhood. Danish Med. Bull., **12**:91, 1965.
6. Plechas, N. P.: Chronic Recurrent Pancreatitis in Childhood. Arch. Surg., **81**:883, 1960.
7. Robechek, P. J.: Hereditary Chronic Relapsing Pancreatitis: A Clue to Pancreatitis in General? Am. J. Surg., **113**:819, 1967.
8. Warwick, W. J. and Leavitt, S. R.: Chronic Relapsing Pancreatitis in in Childhood. J. Dis. Child., **99**:648, 1960.
9. Williams, T. E., Jr., Sherman, N. J. and Clatworthy, H. W., Jr.: Fibrosing Pancreatitis in Childhood. A Cause of Recurrent Abdominal Pain. Pediatrics, **40**:1019, 1967.
10. Williams, W. H. and Hendren, W. H.: Intrapancreatic Duodenal Duplication Causing Pancreatitis in a Child. Surgery, **69**:708, 1971.

Preoperative Endoscopic Cannulation of Pancreatic and Biliary Ducts

MICHAEL KOZOWER, RICHARD A. NORTON, ROBERT E. PAUL, JR.,
KARIM A. FAWAZ, HARRY H. MILLER, ALAN H. ROBBINS, ELIHU M. SCHIMMEL,
HERMAN J. SUGARMAN, JAIME G. TOMAS.

From the Departments of Medicine, Radiology and Surgery, New England Medical Center Hospitals, Boston, Massachusetts, and the Veterans Administration Hospital, Boston, Massachusetts

THE SURGEON who is planning to operate on a patient with jaundice or pancreatic disease needs precise anatomical information regarding the nature of any abnormality present. Within the last few years, endoscopic retrograde cannulation of the papilla of Vater has been developed as a nonoperative method for the study of the pancreatic and biliary duct systems.[2,4,5,8,9,11] This report summarizes our experience with the technic in a 7-month period.

Methods and Materials

Between November 12, 1971 and May 31, 1972, 16 patients with jaundice and clinical symptoms of biliary tract obstruction and one patient with suspected pancreatic carcinoma were referred to us for endoscopic cannulation.

The endoscopic method involves passing a Teflon cannula 1.7 mm. in external diameter through an Olympus JFB duodenoscope into the papilla of Vater, and with injection of 60% meglumine diatrizoate, appropriate ductograms can be obtained. Details of the procedure have been previously described.[8, 9]

Results

Table 1 summarizes the endoscopic and final diagnoses in this group of 17 patients. Thirteen patients underwent exploratory surgery following the procedure. In nine of these patients the endoscopic diagnosis was shown to be correct. In the one patient suspected of having pancreatic carcinoma, changes on the pancreatic ductogram suspicious of malignancy were due to peripancreatic fibrosis following gastric surgery. In three patients the procedure was a failure.

In two patients, both with periampullary carcinoma, the diagnosis was made by the endoscopist. In one of these patients, in addition, a brush cytology of the papillary area was positive.

The following two cases show the value of defining the anatomic lesion prior to operation.

Case Reports

Case 1. A 67-year-old woman weighing 200 pounds underwent cholecystectomy for gallstones in 1957. Postoperatively she developed pancreatitis. Since then she has had recurrent episodes of abdominal pain and jaundice. An intravenous cholangiogram one year ago was negative. She again developed upper abdominal pain and jaundice 2 weeks before the cannulation procedure. Figure 1 shows the retrograde cholangiogram and pancreatogram with a dilated pancreatic duct and a dilated common bile duct containing two stones.

Comment: In this patient, because of her obesity and previous surgery, the demonstration of the abnormalities greatly assisted the surgeon in selecting the type of procedure and in limiting the duration of surgery. The cystic duct remnant containing gravel was removed, a sphincteroplasty was performed, and the two stones were removed.

Case 2. A 39-year-old alcoholic had a history of chronic pancreatitis and underwent drainage of a pseudocyst in 1970. He developed fever, epigastric pain and jaundice 3 weeks before the cannulation procedure. Figure 2 demonstrates both the dilated

---

Submitted for publication June 30, 1972.

Reprint requests: Dr. Richard A. Norton, New England Medical Center Hospitals, 171 Harrison Avenue, Boston, Massachusetts.

TABLE 1.

Endoscopic Diagnosis	Number of Patients	Final Diagnosis Based on Surgery
Cholelithiasis	1	Same as endoscopic diagnosis
Common bile duct calculi	2	Same
Pancreatitis compressing bile duct	1	Same
Periampullary carcinoma	2	Same
Carcinoma of common bile duct	2	Same
Carcinoma of the pancreas	2	One same; one patient with peripancreatic fibrosis
Failures	3	One patient each with cholelithiasis, pancreatic carcinoma; and gallbladder carcinoma
Normal biliary and/or pancreatic tree	4	*Final diagnosis based on liver biopsy and clinical course:* One patient each with drug hepatitis, primary biliary cirrhosis; cholangitis secondary to pancreatitis; and cholangitis
	17	

common bile duct with a distal inflammatory stricture and a segmentally dilated and narrowed pancreatic duct communicating with a pseudocyst containing multiple calculi.

Comment: In this patient, demonstration of the extensive abnormalities within the pancreas assisted the surgeons in selecting a choledochojejunostomy bypass as the procedure with the least mortality and morbidity. The patient has had an uncomplicated recovery.

In four other patients, cannulation of the biliary tree demonstrated no obstruction. This group was then further evaluated with percutaneous liver biopsies. The final diagnoses in this group are summarized in Table 1.

The advantages of being able to avoid operation are illustrated by the third case report.

Case 3. A 47-year-old man had rheumatic heart disease and a history of congestive heart failure. A cholecystectomy for gallstones was performed in 1970. He had episodes of right upper abdominal pain for 3 months, and developed jaundice and pruritus

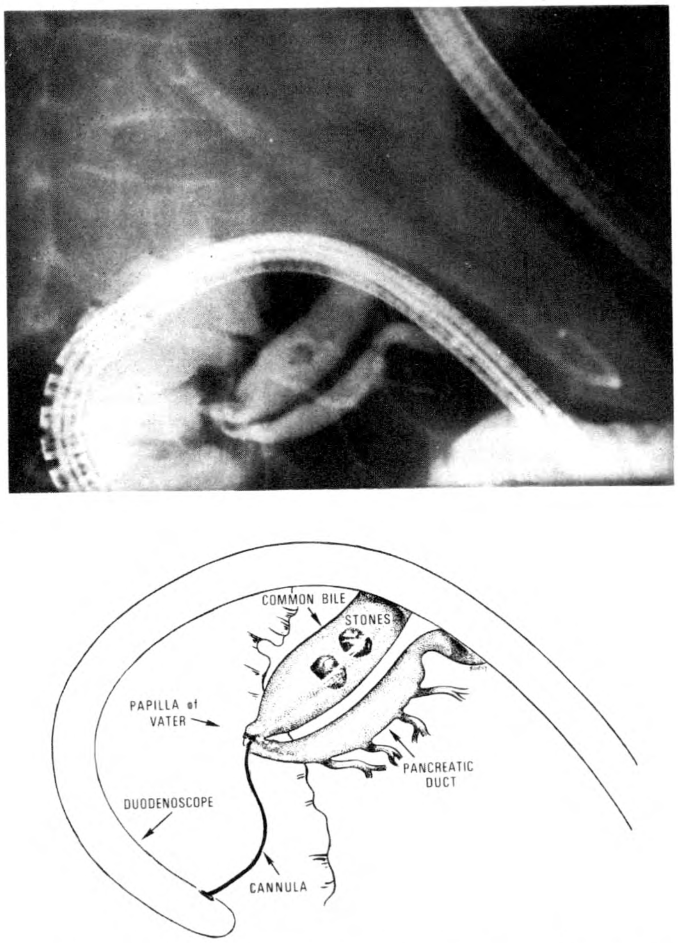


FIG. 1. Retrograde study and illustration showing a dilated common bile duct with two calculi in the distal duct and a dilated pancreatic duct.

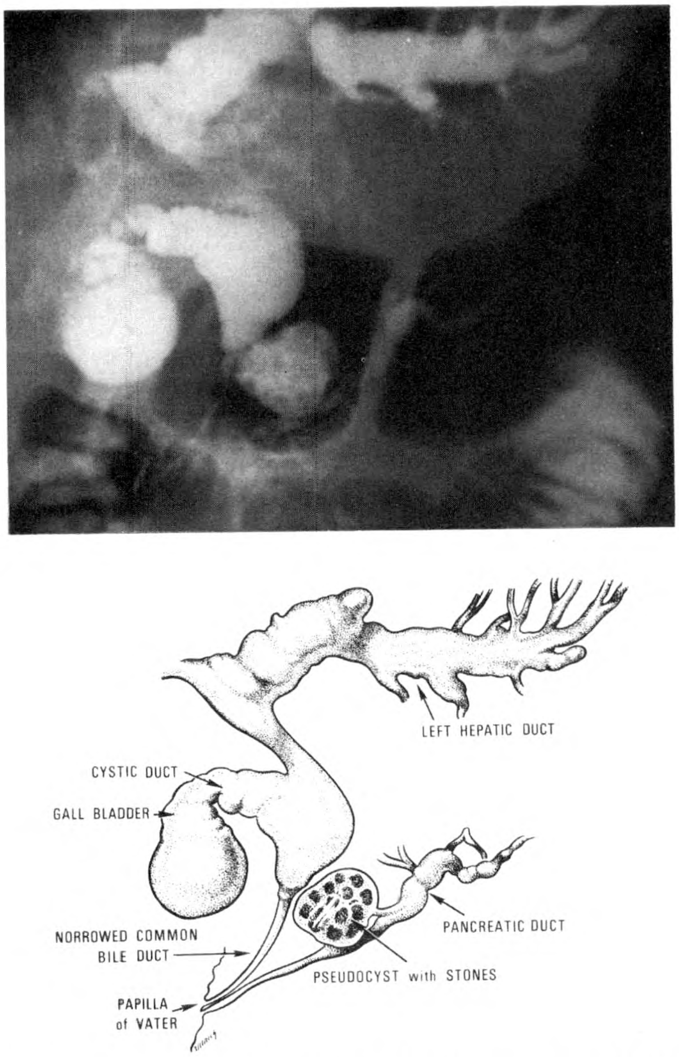


FIG. 2. Retrograde study and illustration demonstrating a dilated common bile duct with a distal inflammatory stricture. The pancreatic duct is dilated with areas of stricture. A pseudocyst with calculi communicates with this duct.

3 weeks before the cannulation procedure. At cannulation a normal common bile duct and biliary tree were demonstrated.

Comment: This man was thought to have choledocholithiasis in view of his history and previous operation. Following the demonstration of a normal biliary tree, a liver biopsy showed cholestasis and focal cell necrosis. This was felt to be compatible with a drug reaction secondary to thiazides. Without the cannulation procedure, he would have required laparotomy or transhepatic cholangiography to exclude extrahepatic biliary obstruction, and the risks of operation would have been increased by the underlying heart disease.[6]

The complications encountered were fever in two patients with a demonstrated biliary tract obstruction. Ascending cholangitis was documented in one of these patients. Elevations in serum amylase levels were noted in three patients with peak amylase elevations of 500, 1000, 1300 Somogyi units respectively. In none, however, was the amylase elevation associated with clinical pancreatitis.

Discussion

There are several advantages of preoperative cannulation. First, a patient with jaundice may prove to have no biliary tract obstruction, and he may then be managed medically. Percutaneous needle liver biopsy may also be performed more safely when the increased risk of bile peritonitis is known to be absent. Also, such a patient is spared the risk of general anesthesia and operation.[1,3]

Second, knowing the nature of a mechanical obstruction helps in the choice of the appropriate surgical procedure. Cases 1 and 2 amply demonstrate this.

Cannulation of the papilla of Vater offers several advantages over transhepatic cholangiography[7] or the "mini-lap."[10] First, it does not constitute an operation or commit the patient to a surgical procedure. Second, it is the only nonoperative method of visualizing the pancreatic duct system. Third, its success rate is independent of whether or not the biliary tree is dilated. Fourth, the complications of bile peritonitis and intra-abdominal hemorrhage are not encountered.

Complications we have seen with cannulation have been few: fever and bacteremia in patients with biliary obstruction, and elevated levels of serum amylase without clinical pancreatitis.

Summary

Preoperative study of the pancreatic and biliary tracts by means of endoscopic cannulation of the papilla of Vater was attempted in 17 patients with jaundice or with suspected pancreatic carcinoma. In four patients surgical intervention was shown to be unnecessary. The remaining 13 patients underwent exploratory surgery; the endoscopic procedure failed to provide a correct diagnosis in only four of these patients. Cannulation of the papilla of Vater not only differentiated between surgical and medical jaundice, but also allowed the surgeon to determine the nature of the anatomical obstruction prior to operation.

Acknowledgment

The authors are greatly indebted to the following clinicians and surgeons for assistance and encouragement with the study: Drs. Frederick Davies, Robert Ewton, Teng Go, Norman Grace, Jeffrey Heilpren, Marshall Kaplan, Donald Nabseth, Melvin Osborne and Lester Williams. The authors wish to acknowledge the instruction and encouragement of Drs. Yoshio Hara and Kazuei Ogoshi, Niigata Hospital, Niigata, Japan. The authors acknowledge Miss June D. Manning's assistance in preparation of the manuscript.

References

1. Beecher, H. K., Todd, D. P.: A Study of Deaths Associated with Anesthesia. Ann. Surg., **140**:2, 1954.
2. Cotton, P. B., Salmon, P. R., Blumgart, L. H., *et al.*: Cannulation of the Papilla of Vater: Assessment of Retrograde Cholangiopancreatography in 60 Patients. Lancet, **1**:53, 1972.
3. Greene, N. M., Bannister, W. K., Cohen, B., *et al.*: Survey of deaths Associated with Anesthesia in Connecticut. Conn. Med. **23**:512, 1959.
4. Jeanpierre, M. M. R., Laurent, J., Bas, M., *et al.*: Catheterisme de L'ampoule de Vater au cours des examens duodenoscopiques. Techniques et resultats. Arch. Fran. Mal. app. Dig., **60**:525, 1971.
5. Kasugai, T., Kuno, N., Aoki, I., *et al.*: Fiberduodenoscopy: Analysis of 353 Examinations. Gastroent. Endosc., **18**:1, 1971.
6. Morrison, D. R.: The Risk of Surgery in Heart Disease. Surgery, **23**:561, 1948.
7. Mujahed, Z., Evans, J. A.: Percutaneous Transhepatic Cholangiography. Radiol. Clin. North Am., **4**:535, 1966.
8. Ogoshi, K., Tobita, Y., Hara, Y.: Endoscopic Observation of the Duodenum and Pancreato-choledochography Using a Duodenal Fiberscope under Direct Vision. Gastroent. Endosc., **12**:83, 1970.
9. Oi, I.: Fiberduodenoscopy and Endoscopic Pancreatocholangiography. Gastroent. Endosc., **17**:59, 1970.
10. Strack, P. R., Newman, H. K., Lerner, A. G., *et al.*: An Integrated Procedure for the Rapid Diagnoses of Biliary Obstruction, Portal Hypertension, and Liver Disease of Uncertain Etiology. N. Engl. J. Med., **285**:1225, 1971.
11. Takagi, K., Ikeda, S., Nakagawa, Y., *et al.*: Retrograde Pancreatography and Cholangiography by Fiber Duodenoscope. Gastroenterology, **59**:445, 1970.

Rupture of the Common Duct and Ampulla of Vater Due to Blunt Trauma

NICHOLAS A. BALSANO, M.D., BENEDICT M. REYNOLDS, M.D., F.A.C.S.

From the Department of Surgery, Misericordia Hospital Medical Center, New York Medical College, Bronx, New York 10466

RUPTURE of the extrahepatic bile ducts from nonpenetrating trauma is an infrequently encountered condition which will tax the ingenuity of the surgeon. Our purpose here is to describe these unique injuries and to outline appropriate methods of management.

The complexity of these injuries is increased by the degree of involvement of the duodenal wall and the main pancreatic duct. The injuries that include the ampullary area are rare, and therefore require special consideration. The following two cases demonstrate specific injuries to the two major areas of the intraduodenal portion of the common and pancreatic ducts.

Report of Cases

Case 1. A 21-year-old man was admitted to the 95th Evacuation Hospital, DaNang, South Vietnam after he had been crushed between two vehicles. On admission the patient complained of generalized abdominal and bilateral flank pain. Physical examination revealed an alert, well developed, well nourished man. Blood pressure was 90/60 mm. Hg, pulse 110–120/min., respiration 20/min. Positive findings were limited to the abdomen where there was generalized tenderness, rigidity and rebound in all quadrants, bowel sounds were absent, exquisite suprapubic tenderness and bilateral costovertebral angle (CVA) pain. Two large bore intravenous catheters were inserted in both upper extremities. Central venous pressure (CVP) monitor, via direct puncture of the subclavian vein, showed an initial pressure of 4 cm H_2O. Insertion of a Foley catheter revealed grossly bloody urine. Initial laboratory data showed Hct 34%, WBC 12,000/$mm.^3$ Chest X-ray was negative, flat plate of abdomen revealed adynamic ileus. Pelvic X-ray showed bilateral fractures of the superior and inferior rami of the pubis. Intravenous pyelogram (IVP) and cystogram were unremarkable.

Approximately 90 minutes after admission an exploratory laparotomy through a midline abdominal incision was performed under general endotracheal anesthesia. The findings at laparotomy were a superficial laceration of the upper pole of the left kidney, a hematoma of the mesentery of the small bowel, and a transection of the common bile duct at the duodenal wall. The defect in the doudenal wall was approximately 2 × 2.5 cm. The ampulla could not be adequately identified nor explored through the duodenal defect. Through a separate anterior duodenotomy 2 cm. in length, adequate exploration of the ampulla revealed transection of the intramural portion of the choledochus. Figure 1 demonstrates the area of injury to the common duct and its relationship to the duodenal wall. The level of injury is at the label of the common duct. The pancreatic catheter was placed to prevent injury to the pancreatic duct; the defect in the duodenum was debrided and closed in two layers. The pancreatic catheter was removed and the anterior duodenostomy was closed in two layers. A primary choledochoduodenostomy was performed to the first portion of the duodenum end-to-side over a #10 soft French rubber catheter inserted through a proximal choledochotomy. The postoperative course was unremarkable. The catheter was removed on the 30th postoperative day.

Case 2. A 30-year-old Vietnamese Captain who was pinned beneath an overturned jeep for approximately 60 minutes, entered the 95th Evacuation Hospital, DaNang, South Vietnam. On admission the patient complained of generalized abdominal pain. Physical examination showed a fully alert male, oriented as to time and place. Blood pressure was 110/60 mm. Hg, pulse 110/min. regular, respiration 20/min. regular. Positive physical findings were limited to the abdomen in which there was generalized abdominal pain and rigidity throughout all quadrants; bowel sounds were absent. Bilateral CVA pain was noted on percussion. Two large bore intravenous catheters were inserted in both upper extremities. A CVP monitor via subclavian vein showed an initial pressure of 6 cm. H_2O. Insertion of a Foley catheter revealed clear urine. Initial laboratory data showed Hct 36%, WBC 8,000. Chest X-ray and flat film of abdomen were negative. IVP was within normal limits. Diagnosis of rupture of intra-abdominal viscus was made and an exploratory laparotomy through a midline abdominal incision was performed. At laparotomy, transections of the common and pancreatic ducts were noted from their duodenal attachments with a 2 cm. tear in the posterior duodenal wall. Figure 1 demonstrates the site of injury to the confluence of ducts labeled CD and pancreatic duct (PD). A pulpy hematoma

---

Submitted for publication September 22, 1972.

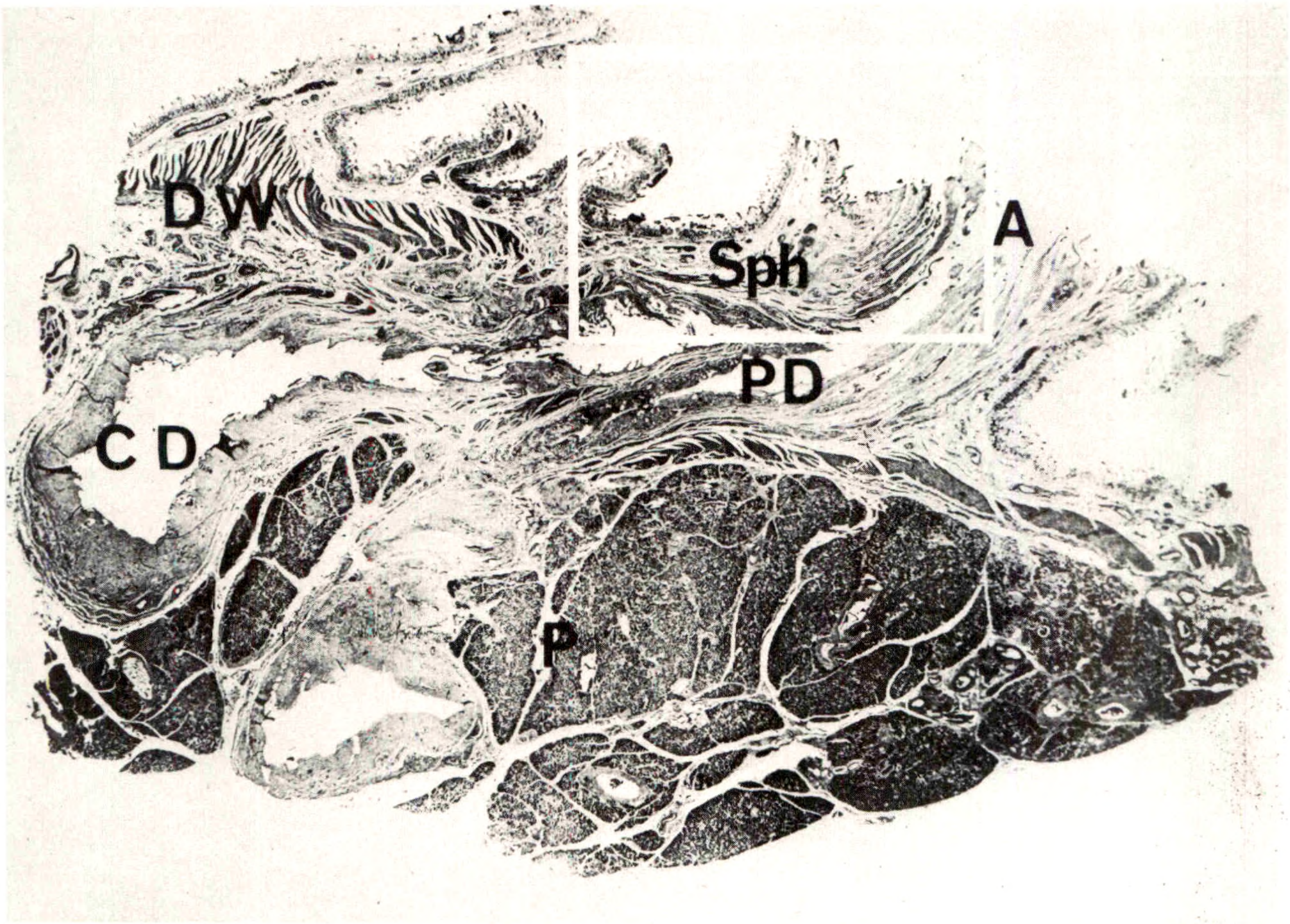


FIG. 1. Photomicrograph demonstrating the confluence of ducts at the ampulla of Vater and their proximity to the duodenal wall.

Sph = sphincter
A = ampulla
P = pancreas
DW = duodenal wall
CD = common duct
PD = pancreatic duct

of the head of the pancreas made the pancreatic duct orifice impossible to identify. Therefore, the pancreas was electively transected over the mesenteric vessels at its superior margin. The major pancreatic duct was identified and opened. The pancreatic duct was cannulated and the torn main ductal orifice was identified in the hematoma and suture ligated (Figs. 2 and 3). The main pancreatic duct drained proximally and distally with a Roux-en-Y loop of jejunum. A primary choledochoduodenostomy to the first portion of the duodenum end-to-side, over a #10 soft French rubber catheter inserted through a proximal choledochotomy, was performed followed by two-layer closure of the lacerated duodenum (Fig. 3). The postoperative course was unremarkable. The French catheter was removed 30 days postoperatively. Upper GI series 3 months post-injury showed patency of the choledochoduodenostomy.

Discussion

Rupture of the extrahepatic bile ducts caused by blunt trauma is rare. The cause of the rupture of the bile passage is nearly always crushing trauma to the right hypochondrial region and especially the right costal margins. This syndrome was first recognized by Fizeau,[9] Mason *et al.*,[12] Fletcher *et al.*,[5] and Hinshaw *et al.*[7] Although injuries to both common and pancreatic ducts are mentioned by Maingot,[11] White and Sanderson,[19] Ehrlick and Howard,[3] no case report describing this as an isolated injury from blunt trauma has been previously reported.

Total transection of the duct can be repaired by primary end-to-end anastomosis, primary choledochoduodenostomy or Roux-en-Y choledochojejunostomy. Injuries to the common bile duct together with or in the vicinity of the main pancreatic duct are the most severe and present the most challenging clinical problem. Search of the literature revealed 12 previously reported cases of complete transection of the common duct at the junction with the duodenum from blunt trauma.[2,5,6,7,9,10,12,13,14,17] Lysaght,[10] performed cholecystogastrostomy and Mast and Oz,[13] performed choledochoduodenostomy while Hinshaw, Turner and Carter,[7] performed a loop choledochojejunostomy and jejunojenostomy for this lesion. Tolins,[17] located the distal severed common duct through

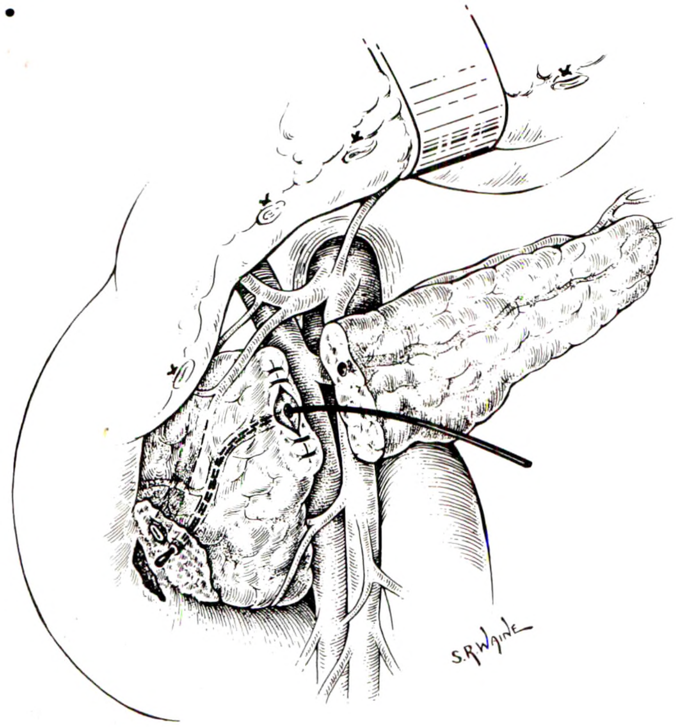


FIG. 2. Transected common bile and pancreatic ducts at the ampulla of Vater. Elective transections of the pancreas with cannulation of the transected major pancreatic duct.

duodenostomy with retrograde probing through the ampulla of Vater and thus was able to perform direct duct-to-duct anastomosis.

The authors feel strongly that insufficient attention has been given to the pancreatic duct in this injury. With complete intramural transection of the common bile duct as presented in the first case report, identification of the pancreatic duct is imperative. Separate duodenotomy may be necessary on the anterior surface of the duodenum to identify the pancreatic duct orifice and facilitate debridement and closure of the duodenal wall at the site of choledochal rupture. With the pancreatic duct cannulated during repair of the defect in the duodenal wall, the likelihood of iatrogenic injury to the duct is minimized. When injuries to the main pancreatic duct occur and remain unrecognized, any of the grave complication of peritonitis, pancreatic abscess, subphrenic abscess, external pancreatic fistula or pseudocyst formation may follow.

The second case reported total transection of both the common bile and pancreatic ducts at the ampulla. The pulpy hematoma of the head of the pancreas make adequate identification of the main pancreatic duct difficult or impossible. Recent literature indicates an increasing interest in the treatment of pancreaticoduodenal wounds by pancreatoduodenectomy.[1,16,18] Under certain circumstances this may be the best method of handling the problem, but alternative conservative approaches should be undertaken whenever feasible.[15] In the second case report the pancreatic injury was localized to the head. The main ductal orifice could not be identified and the pancreas was therefore electively transected at its neck at the region of the mesenteric vessels and the pancreatic duct was identified. A probe was passed into the main duct toward its orifice and the severed duct was identified and suture ligated. A distal reconstruction by a Roux-en-Y loop of jejunum was performed to the ends of the divided pancreatic duct, Figure 3. A sump drain was placed in the operative field. The common duct was reimplanted into the first portion of the duodenum and the laceration of the duodenal wall was closed in two layers. The procedure advocated is the simplest and most conservative approach in treating combined common and pancreatic duct injuries. By transecting the pancreas to identify the duct when it cannot be otherwise identified, we hope to maintain the mortality rate at a low level while preserving pancreatic tissue and preventing significant sequela. This method enables control of the severed duct and a ductal-intestinal anastomosis in a nontraumatized area.

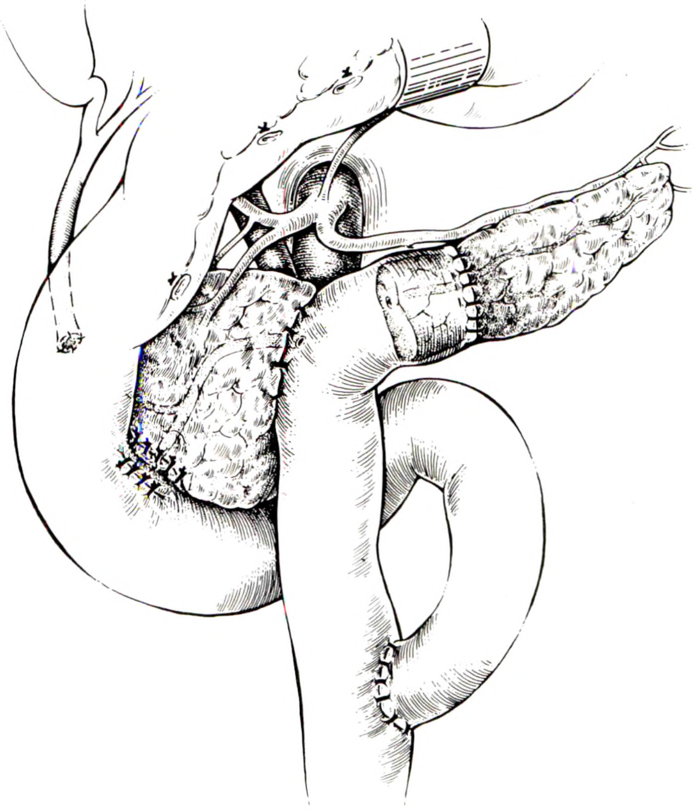


FIG. 3. Diagrammatic sketch of operative procedure. Ligation of the transected proximal pancreatic duct, choledochoduodenostomy and drainage of the proximal and distal pancreatic segments by a Roux-en-Y pancreaticojejunostomy and closure of the duodenal laceration.

Summary

Two cases which demonstrate specific injuries at the intraduodenal portion of the choledochus and the ampulla of Vater due to blunt trauma were reported. The first case involved transection of the intramural portion of the common duct. At this level, exploration of the ampulla to identify the pancreatic duct is imperative to avoid ductal stenosis or occlusion during repair of the duodenal wall.

The second case presented involved avulsion of both the common bile and pancreatic ducts. A pulpy hematoma of the head of the pancreas made identification of avulsed main pancreatic duct difficult. A procedure of elective transection of the pancreas at the neck with identification of the main duct and ligation of the avulsed duct is then performed. The necessary ductal intestinal anastomosis is then completed at the level of pancreatic transection—an area removed from the site of injury.

The major hazard in these unusual injuries relates to the level of avulsion and the involvement of the main pancreatic duct. These cases illustrate the necessary steps of pancreatic ductal identification and drainage of external pancreatic secretion that are essential in the successful management of these complex injuries.

References

1. Bach, R. and Frey, C.: The Management of Pancreatic Trauma. Presented at the meeting of the Society for Surgery of the Alimentary Tract, Chicago, Illinois, June 20, 1970.
2. Donald J. and Donald, John.: Complete Severance of the Common Duct Due to Nonpenetrating Trauma. Ann. Surg., **148**:855, 1958.
3. Ehrlich, E. W. and Howard, J. M.: Apullary Disconnection during Gastrectomy. Ann. Surg., **171**:6, 1969.
4. Fizeau, L.: Observation sur une rupture du conduite choledoque, avec d'eponchement dans leventre; suivie d'autres observations analoques a des reflections sur Ia couleur jauncdes icteriques. J. Med. Cbir. Pbarmacol., **12**:171, 1806.
5. Fletcher, W., Mohnke, D. and Dunphy, J. E.: Complete Division of the Common Bile Duct Due to Blunt Trauma. J. Trauma, **1**:87, 1961.
6. Hartman, S. W. and Greaney, E. M., Jr.: Traumatic Injuries to the Biliary System in Children. Am. J. Surg., **108**: 150, 1964.
7. Hinshaw, D. B., Turner, G. B. and Carter, R.: Transection of the Common Bile Duct Caused by Nonpenetrating Trauma. Am. J. Surg., **104**: 1962.
8. Jordan, G. L. and Beall, A. G.: Diagnosis and Management of Abdominal Trauma. Curr. Prob. Surg., Nov. 1971.
9. Lewis, K. M.: Traumatic Rupture of the Bile Ducts. Ann. Surg., **108**:237, 1938.
10. Lysaght, A. C.: A Case of Traumatic Severance of the Common Bile Duct. Brit. J. Surg., **26**:646, 1939.
11. Maingot, R.: Abdominal Operations, 5th Edition (New York: Appleton-Century-Crofts 1961).
12. Mason, L. B., Sidbury, J. B. and Guiring, S.: Rupture of Extrahepatic Bile Ducts from Nonpenetrating Trauma. Ann. Surg., **140**:234, 1954.
13. Mast, W. L. and Oz, M.: Complete Severance of the Common Bile Duct Due to External Blunt Trauma to the Abdomen. J. Internat. Coll. Surg., **34**:726, 1960.
14. Mohardt, J.: Traumatic Rupture of Common Bile Duct. Report of a Case and Review of the Literature. Quart. Bull. Northwest. Univ. M. School, **30**:16, 1956.
15. Smith, A. D., Woolverton, W. C., Weichert, R. F., III and Drapanas, T.: Operative Management of Pancreatic and Duodenal Injuries. Presented at the meeting of the American Association for the Surgery of Trauma, Chicago, Illinois, Oct. 9, 1970.
16. Thal, A. P. and Wilson, R. F.: A Pattern of Severe Blunt Trauma to the Region of the Pancreas, Surg. Gynecol. Obstet., **119**:773, 1964.
17. Tolins, S. H.: Complete Severance of the Common Bile Ducts Secondary to Blunt Trauma. Ann. Surg., **149**:61, 1959.
18. Wilson, R. F., Tagett, J. P., Pucelik, J. P. and Walt, A. J.: Pancreatic Trauma. J. Trauma, **7**:643, 1967.
19. White, T. W., Sanderson, E. R. and Morgan, A.: Injury to the Sphincter of Oddi in the Course of Gastric and Duodenal Surgery. Am. J. of Surg., **114**: Aug. 1967.

Effects of Parietal Cell Vagotomy on Acid and Pepsin Secretion in Gastric Fistula Dogs

ARI KAYNAN, M.D., GUR BEN-ARI, M.D., ALLAN E. KARK, M.D.,
JACK RUDICK, M.D.*

From the Department of Surgery,
Mount Sinai School of Medicine of the
City University of New York, New York, N.Y. 10029.

SELECTIVE VAGOTOMY of the oxyntic gland area of the stomach (parietal cell vagotomy, highly selective vagotomy) has been advocated for the surgical management of duodenal ulceration.[2,15,18,23,34] In this procedure the vagal innervation to the antrum and pylorus remains intact, allowing normal gastric emptying; a drainage procedure is unnecessary. Theoretically, this should decrease the incidence of postoperative dumping syndrome. Although preliminary clinical results have been encouraging,[2,15,18,23] a disturbing feature has been the fact that acid secretion from Heidenhain pouches in response to feeding is *increased* by this procedure.[1]

The present study was undertaken to determine the effects of parietal cell vagotomy and subsequent truncal vagotomy on gastrin-, histamine-, and vagally-stimulated acid and pepsin output in the intact canine stomach.

Methods

Surgical Procedures

Five mongrel dogs of 18–23 Kg. weight were prepared with gastric fistulas. A Thomas cannula[33] was placed in the corpus of the stomach proximal to the antrum-corpus junction and brought out through the abdominal wall in the midline. Secretory tests were commenced not less than 4 weeks after operation.

Following completion of the control observations, the dogs were subjected to parietal cell vagotomy[1,2] of both the anterior and posterior vagus nerves. Denervation of the stomach was continued distally to 1 cm beyond the antrum-corpus junction, which was determined in initial experiments by the colorimetric method of Moe and Klopper.[24] A ring dissection of the esophagus was effected to ensure complete denervation of the corpus. Only the branches to the antrum and pylorus as well as the extragastric vagi remained intact. Secretory tests were started 3 to 4 weeks later.

At a subsequent operation transthoracic vagotomy was performed through the lower left chest; at this point three major trunks are always seen in the dog. Four weeks later the secretory tests were again repeated.

A gastric drainage procedure was not performed at any stage since this would introduce a variable. Furthermore, drainage procedures, especially gastroenterostomy, have been shown to increase secretion in the dog.[29]

Secretory Stimulants

Three types of secretory stimulants were used:

1. Pentagastrin, the C-terminal pentapeptide of gastrin (Peptavlon, Ayerst Laboratories, New York) in doses of 0.75, 1.5, 3.0, 6.0, and 12.0 µg/Kg.-hr by continuous intravenous infusion.
2. Histamine acid phosphate in doses of 0.25, 0.5, 1.0, 2.0, and 4.0 µg base/Kg.-min. by intravenous infusion.
3. 2-deoxy-d-glucose 100 mg./Kg. intravenously over 10 minutes. This produces a central nervous cytoglucopenia resulting in vagal stimulation.

Experimental Procedures. Experiments were conducted in the conscious state when the animals had been deprived of food for at least 18 hours. Each animal was used not more than two or three times a week, and never

---

Submitted for publication May 8, 1972.

Request Reprints: Jack Rudick, M.D., Mount Sinai Hospital, 11 East 100th Street, New York, N.Y. 10029.

Supported by USPHS Grant #AM 11580 from the National Institute of Arthritis and Metabolic Diseases.

* Career Scientist, New York Health Research Council (I-541).

on successive days. A continuous infusion of 0.9% saline was maintained throughout the experiment to allow for fluid losses. After a 60-minute basal collection, infusion of the stimulant was started. In all studies the drugs were diluted with 0.9% saline and infused intravenously with a Harvard constant infusion pump. Secretion was collected in 10-minute samples for an hour during each dose, allowing for a plateau of secretion at each dose level, and the last three samples were analyzed for acid and pepsin content. In the 2-deoxy-d-glucose experiments, secretion was collected at 10-minute intervals for 2 hours; acid and pepsin were determined in all samples. Administration of the secretory stimulants and of the various doses was randomized; at least three experiments were carried out in every dog with each dose of each stimulant at all stages. Not all doses were used on any 1 day to minimize the possibility of exhaustion.

The volume of gastric secretion was measured in each specimen to the nearest 0.1 ml. Individual samples were analyzed for acid and pepsin. Titratable acidity was determined by titration to pH 7.0 with a Radiometer pH-stat titrator. Pepsin secretion was measured as total peptic activity at pH 2.1, using a modification of Hunt's method[16] with bovine serum albumin substrate, one Hunt unit being equivalent to the peptic activity of 3 µg/ml. of crystalline pepsin (Mann Research Laboratories, New York).

Results are expressed as microequivalents (or units) per minute for pentagastrin and histamine, or milliequivalents (or units) per 10 minutes for 2-deoxy-d-glucose. Statistical significance was determined by the Student's t test.[9]

Results

Secretion of Acid

Pentagastrin (Fig. 1). Denervation of the oxyntic gland area resulted in reduction of the response to submaximal and maximal doses of pentagastrin ($p < 0.05$). When a greater than maximal dose of pentagastrin was administered, the peak acid output could not be restored to the prevagotomy levels. Conversion to a truncal vagotomy caused no further decrease in acid output. In fact, acid output at all doses was higher than for parietal cell vagotomy, falling between control and parietal cell vagotomy values ($p < 0.05$) (Table 1).

Histamine (Fig. 2). The output of acid in response to submaximal and maximal doses of histamine was reduced by parietal cell vagotomy. A larger than maximal dose of histamine restored the peak acid output to control levels obtained with the innervated stomach. In other words, a parallel shift to the right in the dose response curve was obtained for histamine. After truncal vagotomy, the acid output at all doses was slightly higher than for parietal cell vagotomy, but this was not statistically significant ($p > 0.2$).

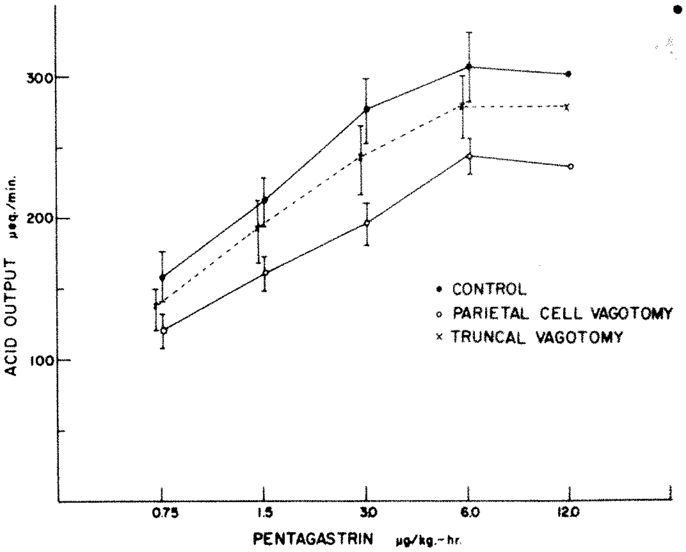


FIG. 1. Effects of parietal cell vagotomy and truncal vagotomy on acid output expressed as μEq/min. in response to graded doses of pentagastrin. In this and in subsequent figures, closed circles refer to control, open circles to parietal cell vagotomy, and crosses to truncal vagotomy. Each point refers to Mean ± Standard Deviation.

2-deoxy-d-glucose. Parietal cell vagotomy decreased the acid output in response to 2-deoxy-d-glucose by 85%. The most striking change was in the peak 10-minute acid output (Fig. 3), but there was a definite response to vagal stimulation. Using either the criteria of Hollander[11] or of Bachrach[3] it was found that *all* the animals had an incomplete vagotomy. When retested after truncal vagotomy, four of the five animals were deemed to have a complete vagotomy. Nevertheless, the peak acid output was not significantly different from the parietal cell vagotomy.

Secretion of Pepsin

The effects on pepsin output in response to all three stimuli were striking. In the control experiments penta-

TABLE 1. *Summary Comparing Effects of Parietal Cell Vagotomy and Truncal Vagotomy on Acid and Pepsin Secretion*

	Parietal Cell Vagotomy		Truncal Vagotomy	
Stimulant	Sub-maximal	Maximal	Sub-maximal	Maximal
Pentagastrin				
Acid	Decreased	Decreased	Decreased (<PCV)	Decreased (<PCV)
Pepsin	Decreased	Decreased	Decreased	Decreased
Histamine				
Acid	Decreased	No Change	Decreased	No Change
Pepsin	Decreased	Decreased	Decreased	Decreased
2-deoxy-d-glucose				
Acid		Decreased		Decreased
Pepsin		Decreased		Decreased

gastrin (Fig. 4) was a more potent stimulant of pepsin secretion than was histamine (Fig. 5). Peak pepsin output was achieved with doses lower than those required for eliciting peak acid output. Both parietal cell vagotomy and subsequent truncal vagotomy markedly reduced pepsin output equally at all doses. Pepsin output was constant after vagotomy regardless of the dose of pentagastrin used. Both types of vagotomy reduced the pepsin responses to histamine equally. The percentage reduction was less than that for pentagastrin but the control values were lower for histamine.

Of the three agents used, 2-deoxy-d-glucose was the most potent stimulant of pepsin secretion. Pepsin output was virtually abolished by parietal cell vagotomy and by truncal vagotomy (Fig. 3). All animals were equally affected. Even the animals in whom a positive acid response was obtained did not secrete a significant amount of pepsin in response to vagal stimulation. In other words, although the vagotomies might have been interpreted as incomplete when applied to acid output, they were complete when applied to pepsin output.

Discussion

The present study clearly demonstrates that parietal cell vagotomy reduces acid output from gastric fistulas in the dog. This is in sharp contrast to acid output from Heidenhain pouches in response to feeding.[1] It has also been shown that the acid response to feeding is increased by truncal vagotomy[7,28,32] or by extragastric vagotomy.[19,20,22,30] The reduction in acid output from the gastric fistula dog is in agreement with the findings of Emas and Grossman[6] for truncal vagotomy and Stening and Grossman[31] for selective gastric vagotomy. The effects on histamine stimulated secretion in the dog represents a parallel shift to the right in the dose response curve for histamine, so that the maximal acid secretory response is unaltered but a larger dose of histamine is required to attain that maximal response. This indicates that the efficacy of histamine is not altered but that vagotomy (parietal or truncal) decreases the affinity of the receptors (involved in acid secretion) for histamine.

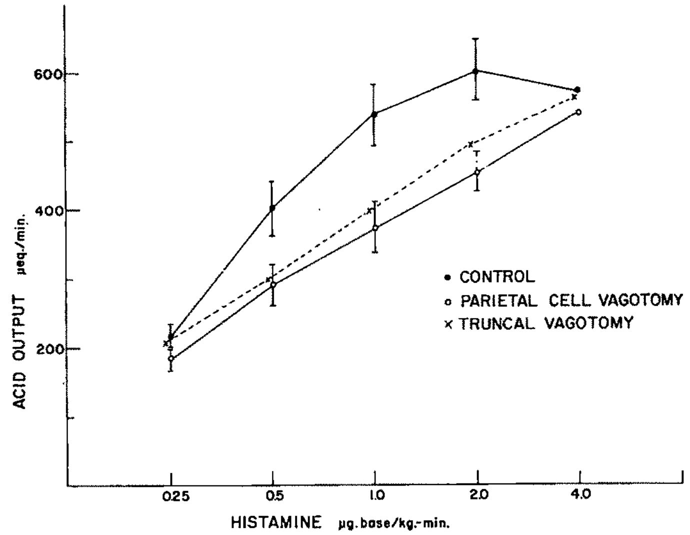


Fig. 2. Effects of parietal cell vagotomy and truncal vagotomy on acid output in response to graded doses of histamine.

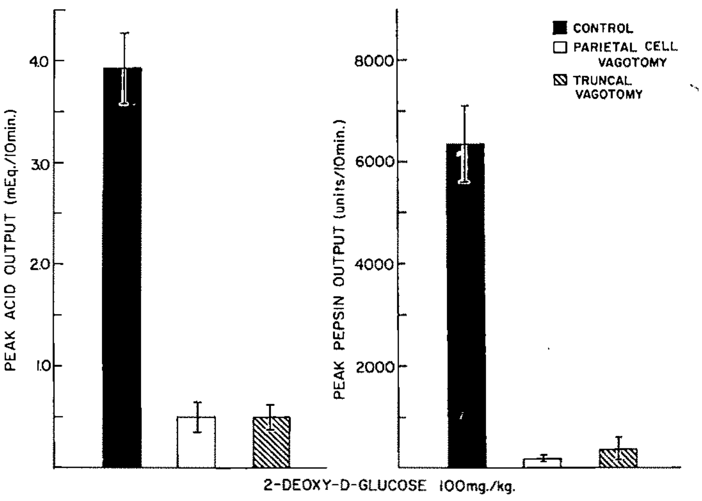


Fig. 3. Acid and pepsin output in response to 2-deoxy-d-glucose before and after parietal cell and truncal vagotomy. Acid output is expressed as mEq/10 min.

It is of interest that parietal cell vagotomy and truncal vagotomy reduced acid responses to histamine equally, yet parietal cell vagotomy significantly reduced acid output in response to pentagastrin to a greater degree than did truncal vagotomy. Similar results were obtained by Stening and Grossman[31] who performed selective gastric vagotomy (preserving only the extragastric fibers) and followed this with a truncal vagotomy. This suggests that there may be a vagally mediated inhibitory reflex operating from the antrum and/or extragastric sources to the oxyntic glands. If so, this reflex would affect only gastrin stimulated secretion. However, there is no direct evidence for such a reflex. It is tempting to implicate secretin, which inhibits gastrin stimulated acid secretion,[10] as the mediator, but there is no evidence suggesting that there is a vagal release of secretin.

Experimental studies in dogs have shown that parietal cell vagotomy maintains normal gastric emptying,[1,17] protects the stomach against histamine induced ulceration[17,25] yet *increases* secretion from Heidenhain pouches.[1] Our studies on the other hand, clearly show a reduction in acid output. The results depend on the type of preparation studied since both parietal cell vagotomy and truncal vagotomy reduce acid output from gastric fistulas, yet both types increase acid output from Heidenhain pouches in response to feeding.[7,28,32]

Reduction of pepsin output was a striking feature of both types of vagotomy. The most potent stimulus of pepsin secretion is vagal stimulation.[13] It is clear that both

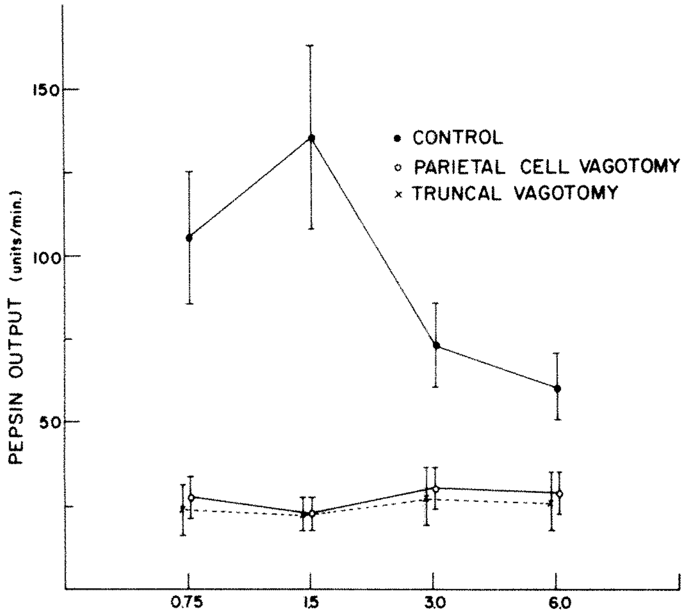


FIG. 4. Pentagastrin stimulated pepsin output before and after both types of vagotomy.

types of vagotomy were equally effective in reducing pepsin output. In all dogs, the response to vagal stimulation was virtually abolished. This is in contrast to acid output, where all five dogs were considered to have an incomplete vagotomy after parietal cell vagotomy. Perhaps pepsin secretion should be used as a test for completeness of vagotomy of the oxyntic gland area.

The persistent acid responses following parietal cell vagotomy may be due to preservation of vagal innervation to the antrum which will result in continuation of the vagal release of gastrin. However, the importance (in terms of magnitude) of the vagal release of gastrin has been questioned.[21]

An unresolved question is the duration of effect of parietal cell vagotomy. Incompleteness of vagotomy remains the most major problem with truncal (or selective) vagotomy. Recovery of function and recurrence of the ulcer diathesis is a not infrequent occurrence after incomplete truncal vagotomy. With parietal cell vagotomy, the stomach is incompletely denervated, although complete denervation of the oxyntic gland area is achieved. Collateral nerve sprouting from the remaining intact vagal fibers[26] may be a cause of late recovery of gastric function following vagotomy. With deliberate incomplete vagotomy[27] new nerve fibers can be seen running parallel to residual degenerating fibers in the wall of the stomach. Clark[4] has demonstrated that as little as 10% of vagal fibers remaining after incomplete vagotomy can result in a full return of vagal activity after a time. It is not clear whether parietal cell vagotomy should be regarded as an incomplete vagotomy in the customary sense. Our experiments were carried over a period of only a few months. Long-term studies are necessary to clarify this problem.

A striking feature of our study with parietal cell vagotomy was the observation that, although acid output in response to all stimuli was reduced, there was a high rate of incompleteness of vagotomy. This was the case whether applying either the original criteria of Hollander[14] or the more recent criteria of Bachrach.[3] Early reports of human studies were enthusiastic about the completeness of vagotomy but more recent reports indicate positive responses to insulin stimulation in excess of 30%.[2,34]

Care must be taken in transposing our data to humans since there may be a species difference, and several aspects must be considered. An increasing number of investigators have performed this procedure for duodenal ulceration, claiming good results. It is worth emphasizing a few points. Not all duodenal ulcer patients are treated with this procedure; only the nonstenosing type are considered appropriate. In fact, any significant scarring of the duodenum is considered a contraindication. In many surgeons opinions this would exclude the majority of duodenal ulcers operated upon. The addition of a drainage procedure or a resection would defeat the purpose of the operation. Reports thus far are premature and, although enthusiastic, give no true indication of the recurrence rate. In a small series, Wastell[34] has reported a 10% recurrence rate with only a 3 to 12 month follow-up. It is not unlikely that the recurrence rate will increase with the passage of time. A further question to be resolved is whether dumping is such a severe problem after vagotomy and drainage; certainly the incidence is lower than with subtotal gastrectomy. Moreover, dumping may occur even in the

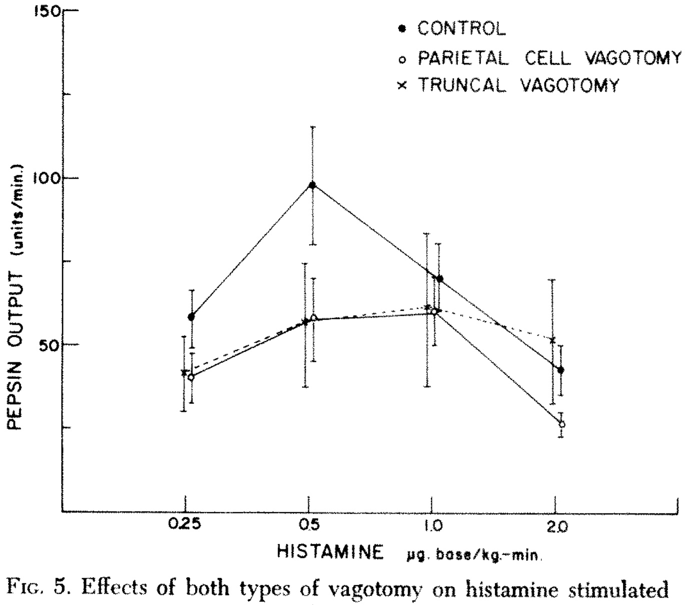


FIG. 5. Effects of both types of vagotomy on histamine stimulated pepsin output.

absence of gastric surgery. Well-controlled clinical studies are necessary to resolve these issues.

Summary

The effects of parietal cell vagotomy and truncal vagotomy on acid and pepsin secretion were studied in five gastric fistula dogs. Parietal cell vagotomy reduced acid output to submaximal and maximal doses of pentagastrin; truncal vagotomy had a similar but slightly less pronounced effect. Acid responses to submaximal but not maximal doses of histamine were equally reduced by both types of vagotomy. Pepsin responses were profoundly suppressed by both. Vagally stimulated acid secretion was markedly reduced but not abolished; vagally stimulated pepsin secretion was virtually abolished by parietal cell vagotomy and by truncal vagotomy.

In sharp contrast to Heidenhain pouch experiments, parietal cell vagotomy (and truncal vagotomy) reduce acid and pepsin output. Previous reports of increase in acid secretion after parietal cell vagotomy must be evaluated in terms of the type of preparation used. It is also concluded that pepsin rather than acid responses should be used as a measure of the completeness of parietal cell vagotomy.

References

1. Amdrup, B. M. and Griffith, C. A.: Selective Vagotomy of the Parietal Cell Mass. Part I: With Preservation of the Innervated Antrum and Pylorus. Ann. Surg., **170**:207, 1969.
2. Amdrup, E. and Jensen, H.-E.: Selective Vagotomy of the Parietal Cell Mass Preserving Innervation of the Undrained Antrum. A Preliminary Report of Results in Patients with Duodenal Ulcer. Gastroenterology, **59**:522, 1970.
3. Bachrach, W. H.: Laboratory Criteria for the Completeness of Vagotomy. Am. J. Dig. Dis., **7**:1071, 1962.
4. Clark, C. G.: Recovery of Gastric Function After Incomplete Vagotomy. Brit. J. Surg., **51**:539, 1964.
5. Dragstedt, L. R., Johnson, A. N. and Singer, E. R.: The Effect of Vagotomy on the Intestinal Phase of Gastric Secretion. Surg. Forum, **11**:336, 1960.
6. Emas, S. and Grossman, M. I.: Response of Heidenhain Pouch to Histamine, Gastrin and Feeding Before and After Truncal Vagotomy in Dogs. Scand. J. Gastroent., **4**:497, 1969.
7. Evans, S. O., Zubiran, J. M., McCarthy, J. D. and Dragstedt, L. R.: Stimulating Effect of Vagotomy on Gastric Secretion in Heidenhain Pouch Dogs. Am. J. Physiol., **174**:219, 1953.
8. Ferguson, D. J., Billings, H., Swenson, D. and Hoover, G.: Segmental Gastrectomy with Innervated Antrum for Duodenal Ulcer. Surgery, **47**:548, 1960.
9. Fisher, R. A.: Statistical Methods for Research Workers. New York, Hafner, 1958.
10. Greenlee, H. B., Longhi, E. H., Delgadillo, J., Nelsen, T. S., El-Bedri, A. L. and Dragstedt, L. R.: Inhibitory Effect of Pancreatic Secretin on Gastric Secretion. Am. J. Physiol., **190**:396, 1957.
11. Griffith, C. A. and Harkins, H. N.: Partial Gastric Vagotomy: An Experimental Study. Gastroenterology, **32**:96, 1957.
12. Hancock, D. M., Joseph, L. B. M., Allen, G. L., Daniel, M. V., Isaac, B. and Prusty, S.: Evaluation of Combined Vagotomy and Segmental Resection for Peptic Ulcer. Indian J. Surg., **19**:233, 1957.
13. Hirschowitz, B. I.: Secretion of Pepsinogen. *In* Handbook of Physiology, Section 6: Alimentary Canal. Vol. II: Secretion (C. F. Code, Ed.). Washington, D.C., American Physiological Society, 1967.
14. Hollander, F.: Laboratory Procedures in the Study of Vagotomy. Gastroenterology, **11**:419, 1948.
15. Holle, F. and Hart, W.: Neue Wege der Chirurgie des Gastro-Duodenal Ulcus. Med. Klin., **62**:441, 1967.
16. Hunt, J. N.: A Method for Estimating Peptic Activity in Gastric Contents. J. Biochem., **42**:104, 1948.
17. Interone, C. V., DelFinado, J. E., Miller, B., Bombeck, C. T. and Nyhus, L. M.: Parietal Cell Vagotomy. Studies of Gastric Emptying and Observations of Protection from Histamine-Induced Ulcer. Arch. Surg., **102**:43, 1971.
18. Johnston, D. and Wilkinson, A.: Selective Vagotomy with Innervated Antrum without Drainage Procedure for Duodenal Ulcer. Brit. J. Surg., **56**:626, 1969.
19. Kelly, K. A., Nyhus, L. M. and Harkins, H. N.: The Vagal Nerve and the Intestinal Phase of Gastric Secretion. Gastroenterology, **46**:163, 1964.
20. Landor, J. H.: The Effect of Extragastric Vagotomy on Heidenhain Pouch Secretion in Dogs. Am. J. Dig. Dis., **9**:256, 1964.
21. McGuigan, J. E. and Trudeau, W. L.: Serum Gastrin: Effect of Vagotomy with Pyloroplasty or with Antrectomy. N. Engl. J. Med., **286**:184, 1972.
22. Middleton, M. D., Kelly, K. A., Nyhus, L. M. and Harkins, H. N.: Selective Vagal Effects on the Intestinal Phase of Gastric Secretion. Gut, **6**:296, 1965.
23. Miller, B., Bombeck, C. T., Schumer, W. and Nyhus, L. M.: Vagotomy Limited to the Parietal Cell Mass: Preliminary Patient Studies. Arch. Surg., **103**:153, 1971.
24. Moe, R. E., Klopper, P. J. and Nyhus, L. M.: Demonstration of the Functional Anatomy of the Canine Gastric Antrum. Am. J. Surg., **110**:277, 1965.
25. Morgenstern, L., Shore, J. M. and State, D.: The Effect of Differential Vagotomy and Segmental Gastric Resection on Histamine-Induced Ulcer in the Dog. Surgery, **57**:721, 1965.
26. Murray, J. G. and Thompson, G. W.: The Occurrence and Function of Collateral Sprouting in the S.N.S. of the Cat. J. Physiol., **135**:133, 1957.
27. Rivilis, J.: Collateral Nerve Sprouting and Gastric Secretory Recovery. Surg. Forum, **20**:317, 1969.
28. Schmitz, E. J., Kanar, E. A., Storer, E. H., Sauvage, L. R. and Harkins, H. N.: Effect of Vagotomy of the Main Stomach on Heidenhain Pouch Secretion. Surg. Forum, **3**:17, 1952.
29. Schmitz, E. J., Kanar, E. A., Storer, E. H., Sauvage, L. R. and Harkins, H. N.: Heidenhain Pouch Secretory Response as Affected by Gastrojejunostomy to the Main Stomach. Proc. Soc. Exp. Biol. Med., **81**:170, 1952.
30. Shiina, E. and Griffith, C. A.: Selective and Total Vagotomy without Drainage. Ann. Surg., **169**:326, 1969.
31. Stening, G. F. and Grossman, M. I.: Gastric Acid Response to Pentagastrin and Histamine after Extragastric Vagotomy in Dogs. Gastroenterology, **59**:364, 1970.
32. Storer, E. H., Schmitz, E. J., Sauvage, L. R., Kanar, E. A., Diessner, C. M. and Harkins, H. N.: Gastric Secretion in Heidenhain Pouches Following Section of the Vagus Nerves to the Main Stomach. Proc. Soc. Exp. Biol. Med., **80**:325, 1952.
33. Thomas, J. E.: An Improved Cannula for Gastric and Intestinal Fistulas. Proc. Soc. Exp. Biol. Med., **46**:260, 1941.
34. Wastell, C., Colin, J. F., MacNaughton, J. I. and Gleeson, J.: Selective Proximal Vagotomy with and without Pyloroplasty. Brit. Med. J., **1**:28, 1972.

Portal Decompression:

Clinical Experience with the "H" Graft

JOSEPH L. GRAZIANO, M.D.* HENRY J. SULLIVAN, M.D.**

From the Surgery and Research Departments, Veterans Administration, Edward Hines, Jr. Hospital, Hines, Illinois

Numerous authors in the past have discussed the necessity for grafting procedures between the portal system and the inferior vena cava.[5, 12, 15, 16] The need usually arises when a side-to-side shunt is indicated but is not technically feasible, because there is either a prominent hepatic caudate lobe or too great a distance between the inferior vena cava and the portal vein.

Experimental studies in dogs support the concept that grafts, whether they are venous or prosthetic, have a high patency when employed as portacaval communications.[4,6,17] Clinically, 20 cases have been reported in the English literature in which venous grafts were used to achieve portacaval decompression[5,8,9,12,14,15,16] (Table 1). In addition, two cases in which teflon prostheses[2,18] were used and 27 with dacron prostheses[3,8] have also been reported (Table 2). The patency of these grafting procedures is listed in the respective tables.

Clinical Material

This communication reports our experience with 13 patients who underwent portal decompressive "H" type shunt utilizing either a segment of autogenous iliac vein (two patients) or a wide caliber dacron prothesis (11 patients). The series consisted of one woman and 12 men ranging in age from 44 to 56 years.

Table 3 summarizes the preoperative liver function studies and general clinical condition prior to operation. Based on this data, ten patients were considered to be good candidates for operation while the remaining three patients (Cases 2, 7, 8) were classified as poor operative risks and were operated upon because of rapid deterioration in their clinical status despite conservative therapy.

Three patients with respiratory complications, secondary to massive ascites, preoperatively underwent autotransfusion of ascitic fluid (Fig. 1). Expansion of their plasma volumes resulted in marked diuresis, serum sodium loss, increase in serum protein levels, and a decrease in the serum aldosterone.

Massive ascites was the indication for operation in six patients and it is to be emphasized that these patients all had undergone prolonged trials of conservative therapy. Seven patients were operated upon because of hemorrhage secondary to ruptured esophageal varices. Three of the seven patients underwent operation after esophageal balloon tamponade failed to control massive variceal hemorrhage.

Operative Findings

All 13 patients had portal hypertension as well as marked increases in pressure from the intrahepatic portion of the portal system (Table 4). Intrahepatic hypertension was demonstrated by manometric recordings taken after clamping the splancnhic side of the portal vein. The indication for a side-to-side shunt was based upon the presence of elevated intrahepatic pressures as demonstrated by this technic.

The necessity for the construction of an "H" type shunt was due to an enlarged caudate lobe in seven cases, too great a spatial distance between the portal vein and the inferior vena cava in four cases, extensive

---

Submitted for publication July 25, 1972.

* Chief, Vascular Surgical Service, Veterans Administration, Edward Hines, Jr. Hospital, Hines, Illinois and Associate Professor, Department of Surgery, Loyola University Medical Center, Maywood, Illinois.

** Senior Cardiothoracic Surgical Resident, Veterans Administration, Edward Hines, Jr. Hospital, Hines, Illinois.

Reprint requests: Research Department, Veterans Administration, Edward Hines, Jr. Hospital, Hines, Illinois 60141.

TABLE 1. *Clinical Use of Autogenous Venous Grafts to Achieve Portasystemic Decompression*

Author	Material	Type	No. Cases	Results
Blakemore, A. H.[1]	Superficial Femoral Vein	P-C	2	No thrombosis of grafts. Pts. left hospital.
Reynolds, J. T.[12]	Azygous Vein	P-C	2	1 pt. died 10 days post-op. of hepatic coma. Graft patent at post-mortem exam. Other pt. did well.
Theron, P.[15]	Femoral Vein	P-C	4	All pts. left hospital. 2 pts. alive 2 yr. post-op and give angiographic evidence of shunt patency.
Theron, P.[16]	Femoral Vein	P-C	5	All grafts patent and have been studied angiographically in some cases.
Forster, E.[5]	Femoral Vein	P-C	3	Patent at 1 yr.
Nay, H. R.[8]	Composite Saphenous Vein	P-C	1	4 mo. post-op. pt. had CVA and died. Graft patent at autopsy.
Rousselot, L. M.[14]	Superficial Femoral Vein	Mesocaval Splenorenal	1 6	All pts. are alive 3–12 mo. post-op.
Nasseth, D. C.[8]	Inferior Vena Cava (2) Saphenous Vein (1)	P-C	3	All pts. are alive. Saphenous graft clotted and had to be replaced by a mesocaval shunt.
Present Communication	Iliac Vein	P-C	2	One pt. died 8 mo. post-op. Graft patency was not determined. The other graft thrombosed.

P-C = portacaval shunt

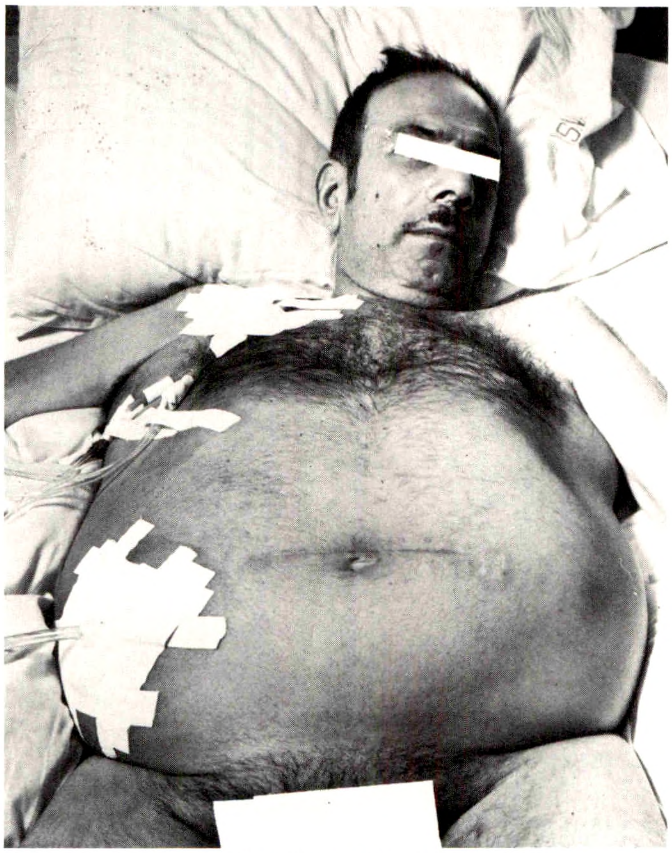


FIG. 1A. Mr. M .A. (Case 1) preoperatively undergoing ascitic fluid autotransfusion.

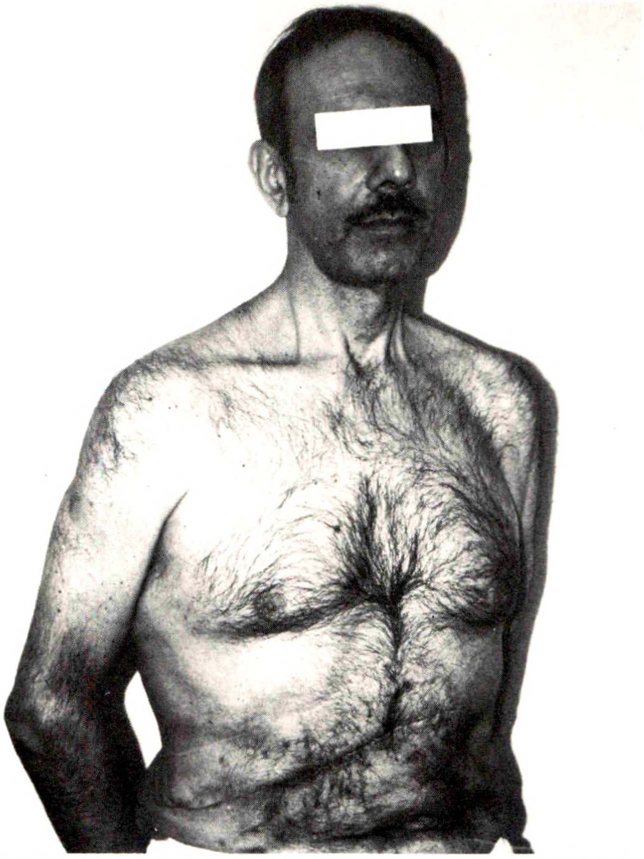


FIG. 1B. Mr. M. A. (Case 1) postoperatively after an "H" type portacaval shunt was constructed utilizing a 22 mm. dacron prosthesis. Followup at 14 month reveals no accumulation of ascitic fluid.

scarring of the porta hepatis as a result of previous operation in one patient, and a partially thrombosed portal vein in one patient. This last patient underwent a mesocaval shunt utilizing a 12 mm. dacron prothesis. Portacaval shunts were constructed in the remaining 12 patients—two with autogenous iliac vein and ten with wide caliber dacron protheses.

Surgical Technic

The following major points are emphasized concerning technic: (Fig. 2)

TABLE 2. *Clinical Experience with Prosthetic Portasystemic Shunts*

Author	Material	Type	No. Cases	Results
Dale, W. A.[2]	Teflon	P-C	1	Graft patent 2 yr. post-op. at angiography
Yeoh, K. S.[18]	Teflon	P-C	1	Initial function good. 6 mo. post-op. episode of hematemesis.
Nabseth, D. C.[8]	Dacron	P-C	2	Patent 22 mo. post-op. at angiography.
Drapanos, T.[3]	Knitted Dacron	M-C	25	22 pts. alive at mean follow up of 19 mo. All shunts were patent.
Present Communication	Knitted Dacron	P-C (11) M-C (1)	12	10 pts. alive at average time of 1 yr. No evidence of shunt occlusion.

P-C = portacaval shunt
M-C = mesocaval shunt

TABLE 3.

Cases	Albumin	Bilirubin	BSP %	Prothrombin Time %	HGB (Gm.)	Ascites	Nutrition	Episodes of Esophageal Hemorrhage
1. M. A.	3.4	1.5	10	60	13.0	massive	good	0
2. W. D.	2.5	5.0	42	50	12.0	moderate responds to diuretics	fair	1
3. H. F.	3.2	2.0	25	60	10.0	moderate	good	2
4. A. M.	3.1	2.0	20	50	8.6	none	fair	1
5. J. M.	3.0	2.2	16.5	50	12.5	massive	fair	0
6. J. O.	3.2	1.2	17	60	11.0	none	good	1
7. J. O.	2.4	2.5	30	40	10.0	massive	poor	0
8. A. R.	2.4	2.1	29	55	11.5	moderate	poor	1
9. D. R.	3.0	1.0	15	70	12.0	massive	good	0
10. A. T.	3.2	1.2	18	38	12.5	massive	good	2
11. A. T.	3.5	1.8	20	50	9.0	none	fair	3
12. G. R.	3.8	2.0	15	70	12.0	none	good	2
13. A. L.	3.5	1.0	15	80	11.0	massive	fair	1

1. A large right subcostal incision crossing the midline provides satisfactory exposure.
2. Knitted dacron protheses of at least 22 mm. in diameter are rigid enough to maintain their shape yet are sufficiently pliable to conform to anatomic variants.
3. Elliptical window defects, 4–6 mm. in width, are created in both the portal vein and the inferior vena cava to assure graft patency. The defect created in the inferior vena cava is made on the anterior surface of the vein, in an oblique longitudinal axis, and superior to the entrance of the left renal vein.
4. The graft would be anastomosed first to the portal

TABLE 4.

Cases	Portal Pressure Pre-shunt	Portal Pressure with Occlusion of Portal View	Portal Pressure Post-shunt	Indication for "H" Shunt	Type of Operation	Indication for "H" Graft
1.	380	340	125	prominent caudate lobe	portacaval	22 mm. dacron
2.	410	320	170	prominent caudate lobe	portacaval	19 mm. dacron
3.	380	210	180	prominent caudate lobe	portacaval	22 mm. dacron
4.	A. 420	390	300	spatially unable to reach	portacaval	iliac vein
	B. 440	390	250		portacaval	22 mm. dacron
5.	320	300	215	portahepatis scarred 2 to gastrectomy	portacaval	22 mm. dacron
6.	330	320	220	spatially unable to reach	portacaval	22 mm. dacron
7.	390	310	230	portal vein thrombosed	mesocaval	12 mm. dacron
8.	380	300	150	prominent caudate lobe	portacaval	iliac vein
9.	340	300	130	prominent caudate lobe	portacaval	22 mm. dacron
10.	320	280	120	spatially unable to reach	portacaval	22 mm. dacron
11.	400	375	180	spatially unable to reach	portacaval	22 mm. dacron
12.	420	400	160	prominent caudate lobe	portacaval	22 mm. dacron
13.	380	350	140	prominent caudate lobe	portacaval	22 mm. dacron

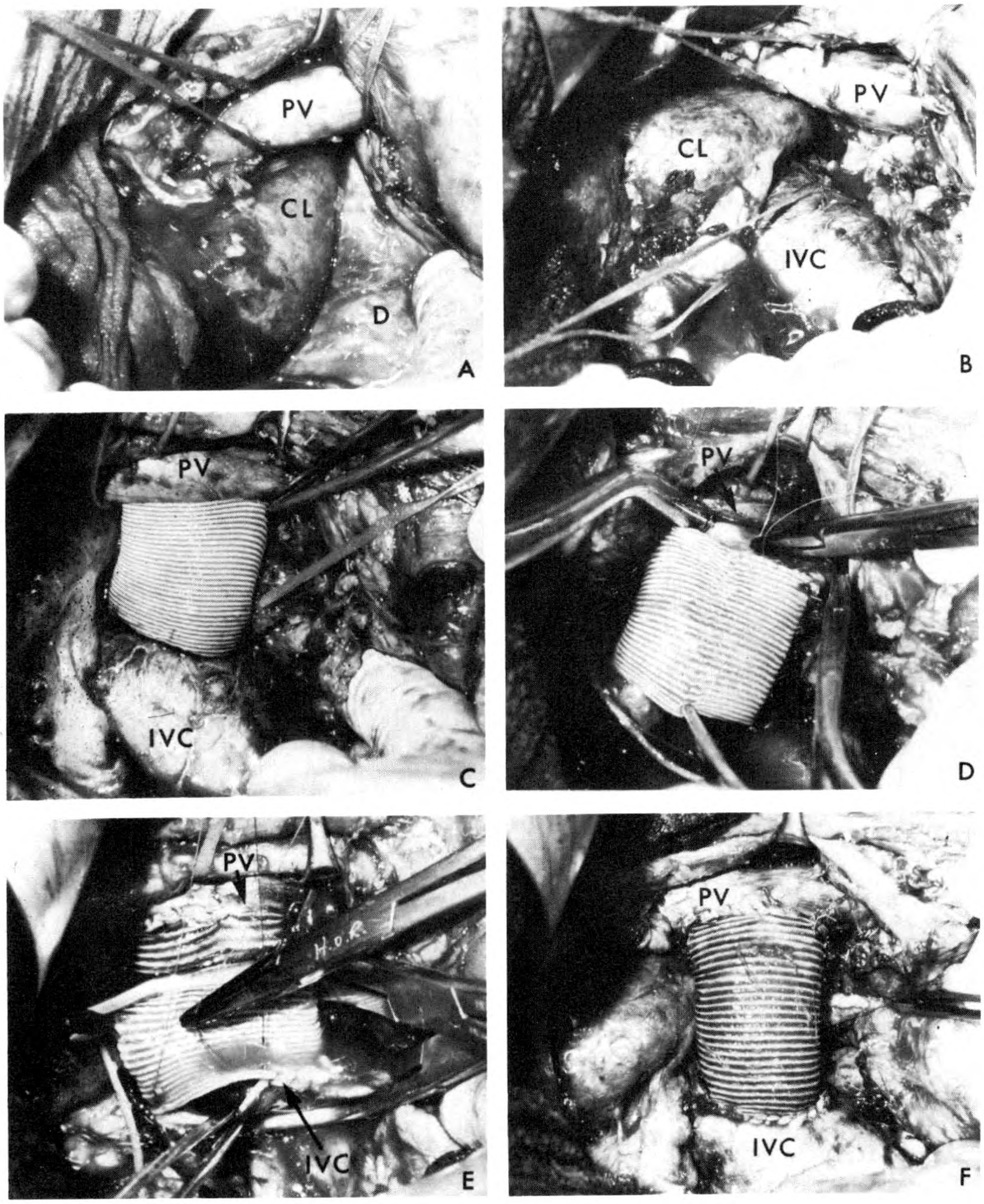


FIG. 2. A. Initial dissection of the portal vein. B. Enlarged caudate lobe of the liver interposed between the portal vein and the inferior vena cava. C. Measuring of the dacron graft. D. Anastomosis of the dacron graft to the portal vein. E. Anastomosis of the dacron graft to the inferior vena cava. F. Graft in place and filled with blood. PV = portal vein, CL = caudate lobe, D = duodenum, IVC = inferior vena cava.

vein and then to the inferior vena cava since the portal vein has limited mobility.

Results

Two patients died in the immediate postoperative period (Cases 2 and 7 in Table 3). Mr. W. D. (Case 2) died 6 days postoperatively in hepatic coma. There was no evidence of recurrent variceal hemorrhage, however, no post-mortem examination was obtained. In Mr. J. O. (Case 7), 2800 cc. of blood were found in the peritoneal cavity at autopsy. The graft was patent and the anastomosis was intact. The possibility of a coagulation defect is a consideration.

Mrs. A. R. (Case 8) died approximately 8 months postoperatively of massive gastrointestinal hemorrhage and hepatic failure. No post-mortem examination was obtained to evaluate the patency of the autogenous iliac vein used as an "H" graft.

Mr. A. M. (Case 4) initially underwent construction of an "H" type shunt utilizing an autogenous iliac vein. Twenty-four hours postoperatively, the patient had recurrent massive upper gastrointestinal hemorrhage secondary to ruptured esophageal varices, as demonstrated by endoscopy. At the time of reoperation, the graft was found to be thrombosed and it was replaced by a 22 mm. segment of woven dacron. At 20 months follow-up the patient has returned to work and has had no recurrence of gastrointestinal hemorrhage. His liver function tests have slightly improved compared to preoperative levels.

The remaining nine patients had uneventful postoperative courses and were discharged from the hospital improved.

Follow-up

In the ten surviving patients the follow-up period has ranged between 2 months and 2½ years (mean 1 year). The five patients operated upon because of intractable ascites had evidence of minimal reaccumulation of ascitic fluid, in the immediate postoperative period. This was evidenced by an increase in weight gain (average 3 pounds) as well as a 1 to 2 inch increase in the abdominal circumference. These gains were lost within a 2-week period. Upon discharge these patients were not given diuretics or restricted in fluid intake; however, a low sodium diet was recommended. Up to the present time there has been no evidence of ascitic fluid recurrence. In the five surviving patients who were operated upon because of variceal hemorrhage there have been no episodes of recurrent bleeding.

Six of the ten surviving patients have been evaluated angiographically for shunt patency (Fig. 3). The technic consisted of femoral vein catheterization of the shunt via the Seldinger method in five instances and umbilical vein catheterization and angiography in the remaining case. All of the patients studied were found to have widely patent shunts.

Discussion

The purpose of this communication is not to discuss the merits of a side-to-side rather than an end-to-side portacaval shunt. Several authors have already stressed the usefulness of side-to-side portal decompression in intrahepatic hypertension[7, 10, 13] and believe it to be the procedure of choice for intractable ascites.[11]

The "H" type portosystemic shunt offers an adequate alternative for patients who require side-to-side decompression which is precluded by technical factors. In some instances the use of an "H" graft presents technical advantages over a difficult side-to-side shunt.

Summary

Our experience with 13 patients who underwent portacaval "H" type shunts, utilizing either a segment of autogenous vein or a dacron prothesis, is reported. Ten patients are alive and have no clinical evidence of shunt occlusion. Six patients have been studied angiographically and patency of the shunts has been demonstrated in all instances.

From both experimental and clinical studies that have been reviewed, in addition to our present experience, the dacron prosthetic "H" type graft would seem to be an alternative treatment for patients requiring side-to-side shunts when technical aspects make the procedure extremely difficult if not impossible.

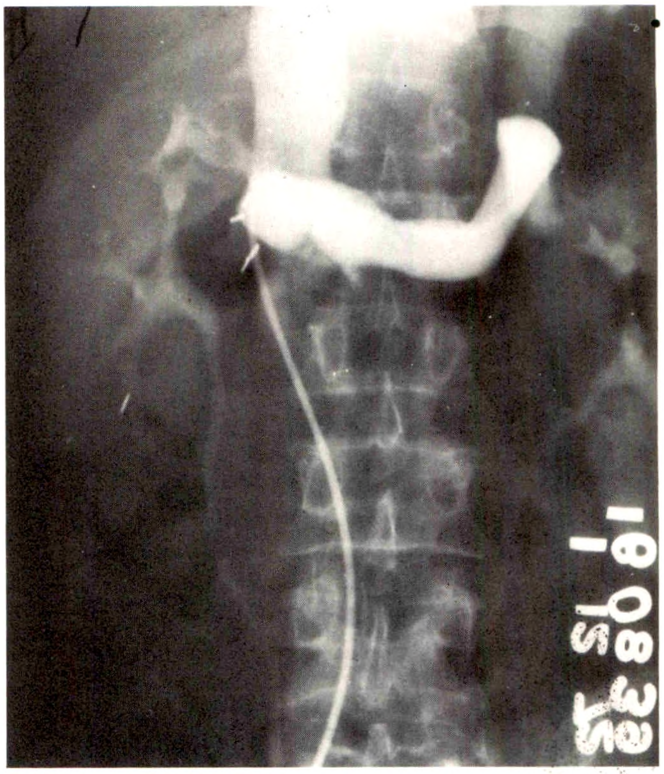


FIG. 3. Angiographic demonstration of "H" type shunt patency in patient A. T. (Case 10). A catheter is passed via the Seldinger technic through the femoral vein, inferior vena cava, and 22 mm. dacron graft. Injection of dye reveals good visualization of the splenic vein.

References

1. Blakemore, A. H. and Fitzpatrick, H. F.: The Surgical Management of the Post Splenectomy Bleeder with Extrahepatic Portal Hypertension. Ann. Surg., **134**:420. 1951.
2. Dale, W. A. and Scott, H. W.: Grafts of the Venous System. Surgery, **53**:52, 1963.
3. Drapanas, T.: Interposition Mesocaval Shunt for Treatment of Portal Hypertension. Ann. Surg., **176**:435, 1972.
4. Escamilla, H. and Ellis, P. R., Jr.: A Porta-Caval Communication Utilizing a Tubular Teflon Prosthesis. Surg. Gynec. Obstet., **116**:529, 1963.
5. Forster, E., Kunlin, J., Schnoebelen, R., Coblenze, J., and Muller, J.: Portacaval Anastomoses by Venous Graft with Suture Suspended by Loops. Mem. Acad. Chir., **87**:797, 1961.
6. Foster, J. H., Jolly, P. C., Symbas, P. N. and Dively, W. L.: Vein Grafting in Portal Venous System. Surgery, **50**:97, 1961.
7. Longmire, W. P., Jr., Mulder, D. G., Mahoney, P. S., and Mellinkoff, S. W.: Side-to-side Portacaval Anastomosis for Portal Hypertension. Ann. Surg., **147**:881, 1958.
8. Nabseth, D. C., O'Hara, T. E., Marks, L. J., Mehrez, I. O.: The "H" Graft in Portacaval Shunts. Am. Surg., **168**:201, 1968.

9. Nay, H. R., and Fitzpatrick: A Study of Various Types of Superior Mesenteric Vein—Inferior Vena Cava Shunts Via Composite Grafts. Surgery, **59**:540, 1966.
10. Orloff, M. J. and Snyder, G. B.: Experimental Ascites. II. The Effects of Portacaval Shunts on Ascites Produced with an Internal Vena Cava Cannula. Surgery, **50**:220, 1961.
11. Orloff, M. J.: Effect of Side-to-Side Portacaval Shunt on Intractable Ascites, Sodium Excretion, and Aldosterone Metabolism in Man. Am. J. Surg., **112**:287, 1966.
12. Reynolds, J. T. and Southwick, H. W.: Portal Hypertension. Use of Venous Graft When Side-to-Side Anastomosis is Impossible. Arch. Surg., **62**:789, 1951.
13. Reynolds, T. B., Mikkelsen, W. P., Redeker, A. G., and Yamahiro, H. S.: The Effect of a Side-to-Side Portacaval Shunt on Hepatic Hemodynamics in Cirrhosis. J. Clin. Invest., **41**:1242, 1962.
14. Rousselot, L. M.: Autogenous Vein Grafts in Spleno Renal Anastomosis. Surgery, **31**:403, 1952.
15. Theron, P.: The Portacaval Shunt Operation with Special Reference to the Use of Vein Grafts. S. Afr. J. Med., **27**:73, 1953.
16. Theron, P. and Allan, J. C.: Ascites, A Clinical and Experimental Study. Acta. Med. Scandinav., **152**:145, 1955.
17. Symbas, P. H., Foster, J. H., and Scott, H. W., Jr.: Experimental Vein Grafting in the Portal Venous System. Surgery, **50**:97, 1961.
18. Yeoh, K. S. and Eiseman, B.: Portal Vein Thrombosis: Thrombectomy and Portacaval Anastomosis with the Use of a Graft. Singapore Med. J., **3**:64, 1962.

Weight Loss Following Thermal Injury

THOMAS W. NEWSOME, M.D., MAJOR, MC,* ARTHUR D. MASON, JR., M.D.,
BASIL A. PRUITT, JR., M.D., COL, MC

From the United States Army Institute of Surgical Research,
Brooke Army Medical Center,
Fort Sam Houston, Texas 78234.

THE SEVERE WEIGHT LOSS frequently associated with thermal injury has been attributed to a combination of hypermetabolism and inadequate caloric intake. Energy expenditures as much as twice normal have been documented during the first 3 weeks after such injury,[2,7] and negative nitrogen balance may persist for 5–6 weeks.[5] At the same time, oral alimentation may be restricted by prolonged ileus, disorientation, facial burns, associated injuries, or the need for respiratory support via an endotracheal or tracheostomy tube. Prior to the recent development of technics for intravenous hyperalimentation, administration of nutrients by the venous route was also limited. Even with the administration of 4,000–8,000 calories per day by a combination of intravenous and oral routes, actual weight gain is seldom achieved in the first few weeks postburn, although weight stabilization may be attained.[6]

Most of the studies of this catabolic phase of burn injury have been confined to intensive but brief monitoring of oxygen consumption, evaporative water loss, and body weight in relatively small numbers of patients during the first 3 weeks postburn. Soroff's[5] study of nitrogen balance is the only long-term analysis of postburn metabolism and it was limited to patients with burn sizes of 20–35%.

In order to define the temporal pattern of postburn weight loss and determine its relation to burn size, we have divided a selected patient population according to burn size and analyzed their weight changes over a 3-month postburn period.

Methods

A retrospective analysis was made of the weight records of 1,028 patients admitted to the United States Army Institute of Surgical Research burn unit between December 1967 and November 1970. This time period was chosen because it immediately preceded the initiation of high caloric parenteral feedings. Eighty-six patients with reliable preburn weights, serial weight assessments postburn, and without major amputations were consolidated into three burn-size ranges of 0–19% (17 patients), 20–39% (25 patients), and 40+% (44 patients). Patient ages ranged from 2–70 years with the greatest number in the 15–40 year range.

Each patient had been weighed on a Toledo 100 Kg. scale with 50 Gm. graduations. Weekly weights from the time of admission to the eighth week postburn were recorded in the 0–19% and 20–39% ranges. At 12 weeks postburn no patients with burns under 20% and only four patients with 20–39% burns remained hospitalized. Hospital discharges occurred later in patients with burns of more than 40% and weight data of this group were recorded at 12 weeks. Those weights obviously biased by dressings were discarded. For comparison, all weights were expressed as per cent of preburn weight.

For each time period, the three data groups were subjected to a preliminary analysis of variance. In those periods where significant ($p < 0.05$) intergroup differences were detected, all possible comparisons of differences between individual groups were tested for significance ($p < 0.05$) by the technic of Scheffe.[4]

Hospital records were also used to determine, for each burn size group, the mean date of wound coverage by reepitheliazation and/or autografting.

Results

Figure 1 shows a distinct pattern of weight loss following thermal injury in which both extent and duration of loss are proportional to burn size.

Submitted for publication August 31, 1972.

* Present address: 6515 Orchid Lane, Dallas, Texas 75230.

Request reprints: Library Branch, US Army Institute of Surgical Research, Brooke Army Medical Center, Fort Sam Houston, Texas 78234.

In the 17 patients with burns covering less than 20% of the total body surface, mean weight loss was 3.5% one week postburn. The maximum loss of 6% occurred 3 weeks after injury. Weight gain began at the fourth week and return to preburn weight was recorded at 8 weeks. Wound coverage in this group was attained at a mean time of 33 days postburn.

In 25 patients with burn sizes from 20–39%, significant weight loss did not appear until the second week postburn (6%) and the maximum decrease of 12% was not reached until the end of the fourth week. Modest weight gains were noted at 6 and 8 weeks. Mean time of wound coverage in this group was the fortieth postburn day.

In the 44 patients with burns of more than 40% there was a 4% weight loss at 1 week, a 10% loss at 2 weeks, and a continuing loss until a maximum of 22% was reached at 8 weeks. In the survivors still hospitalized 12 weeks after injury there was a wide range of weight loss, but the mean weight loss was smaller than at 8 weeks. Wound coverage was completed at a mean time of 57 days postburn in this group.

Statistical analysis of intergroup weight differences demonstrated persistent significant difference between the mean per cent of preburn weight of patients with burns of under 20% and that of patients with burns of over 40% at all times beyond the first week postburn. The difference between patients with less than 20% burns and those with 20–39% burns did not achieve significance until the fourth week, while the difference between the latter group and patients with greater than 40% burns was not significant until the eighth week.

Examination of the weight curves (Fig. 1) reveals that weight stabilization occurred approximately 2 weeks prior to completion of wound coverage in both the 0–19% and 20–39% groups and that 2 weeks prior to wound closure in the 40+% group the rate of weight loss flattened. Weight gain was subsequently associated with wound closure in all groups.

Discussion

These data define a temporal pattern of weight loss following thermal injury in which the magnitude and duration of loss are directly related to the severity of injury.

A metabolic study closely paralleling this review is that of Soroff[5] in which nitrogen balance was carefully monitored over a 3-month period in 11 patients with burn wounds of from 20 to 35% of the total body surface. Although nitrogen requirements did not return to control levels until 60–70 days postburn, a positive cumulative nitrogen balance was reached between 30–39 days with the use of high protein dietary supplements. This latter figure correlates reasonably well with the 28-day point at which the mean weight stabilized in our study group with burns of from 20 to 39% of the total body surface. The failure of this group to achieve more than modest weight increase over the next 4 weeks may confirm the persistence of significant catabolism suggested by Soroff's data.

TABLE 1. *Intergroup Statistical Comparisons*

Postburn Week	A–C	A–B	B–C
1	NS	NS	NS
2	*	NS	NS
3	*	NS	NS
4	**	*	NS
6	*	NS	NS
8	**	*	*

Group A—0–19% burns
Group B—20–39% burns
Group C—40 + % burns
Significance: NS—not significant
* —$0.01 < p < 0.05$
**—$0.001 < p < 0.01$

The relation of wound closure to postburn metabolic rates has been the focus of several studies which have documented concomitant increases in both oxygen consumption and evaporative water loss in the early weeks postburn.[1-3,7] Because of the calculated magnitude of daily evaporative water loss from the burn wound into a normally humidified environment (2 Gm./Kg./% burn[3]) and the measured heat cost of vaporization of 0.58 calories/Gm. at 30°C., a causal relationship between evaporative loss and postburn hypermetabolism has been hypothesized. This does not, however, appear to be a simple relationship, for Zawacki, *et al.*[7] have shown that diminishing evaporative loss over a 12-hour period does not alter the metabolic rate. Gump

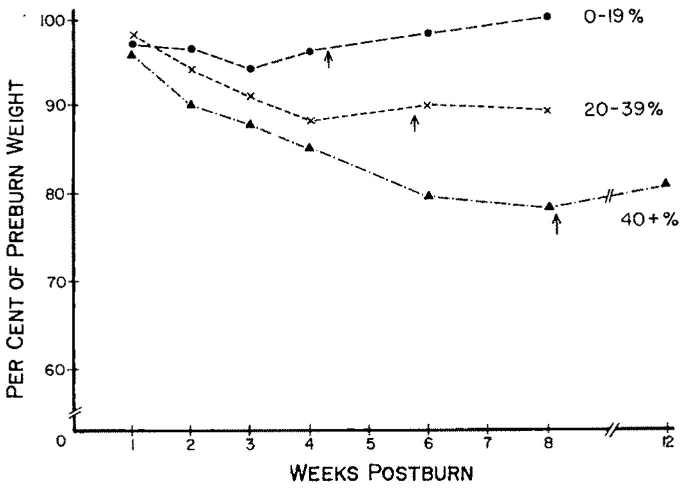


FIG. 1. Mean weight following thermal injury in three burn-size ranges is plotted as a per cent of preburn weight. Arrows mark the mean time of wound closure for each range.

and Kinney[2] have presented additional data suggesting that while evaporative losses decline during the first 2 weeks, the metabolic rate rises. In contrast is a report from Sweden[1] that postburn metabolic rates are decreased by a warm, dry environment which may provide a portion of the heat required for vaporization. Clouding interpretation of this study is the fact that the control temperature of 22°C. used for contrast is sufficiently low to enhance pretreatment hypermetabolism.

Definitive wound closure, defined as the completion of reepitheliazation and/or autografting of the burn wound, followed weight stabilization by almost 2 weeks in each of the burn size ranges considered. At the time when reversal of weight loss occurred, however, coverage of significant portions of the burn wound had already been effected in most patients by a combination of reepitheliazation of second degree burn and allografting of third degree burn. Whether such closure bears a causal relationship to the reversal of weight loss cannot be determined from our data, since the patient groups did not include individuals in whom such coverage was deliberately delayed. Our data do show that final wound closure, like weight stabilization, occurs later as burn size increases.

Metabolic stimuli other than the open wound are active in the burn patient and probably relate to burn size. Among these are hyperdynamic circulation, elevated catecholamines, and sepsis. As the burn wound heals, these ebb, and the patient's metabolic demands diminish.

Since both the magnitude and the duration of the catabolic phase following burn injury seem clearly related to the extent of injury and are difficult to effectively mute, emphasis must be placed on supplying the patient with a caloric intake adequate to achieve net caloric balance. The effectiveness of vigorous oral and intravenous caloric support has been the subject of a recent report from this institute by Wilmore, et al.[6]

Summary

A pattern of weight loss has been found in patients with thermal injuries. The magnitude and duration are directly related to the extent of injury. A maximum mean loss of 22% of preburn weight occurred 8 weeks postburn in patients with burns covering more than 40% of the total body surface. Weight stabilization preceded definitive wound closure and was considered to reflect diminishing metabolic demands.

References

1. Barr, P.-O., Liljedahl, S.-O., Birke, G. and Plantin, L.-O.: Oxygen Consumption and Water Loss During Treatment of Burns with Warm Dry Air. Lancet, 1:164, 1968.
2. Gump, F. E. and Kinney, J. M.: Energy Balance and Weight Loss in Burned Patients. Arch. Surg., 103:442, 1971.
3. Harrison, H. N., Moncrief, J. A., Duckett, J. W., Jr. and Mason, A. D., Jr.: The Relationship Between Energy Metabolism and Water Loss from Vaporization in Severely Burned Patients. Surgery, 56:203, 1964.
4. Ostle, B.: Statistics in Research, Iowa State College Press, 1958.
5. Soroff, H. S., Pearson, E. and Artz, C. P.: An Estimation of the Nitrogen Requirements for Equilibrium in Burned Patients. Surg. Gynecol. Obstet., 112:159, 1961.
6. Wilmore, D. W., Curreri, P. W., Spitzer, K. W., Spitzer, M. E. and Pruitt, B. A., Jr.: Supranormal Dietary Intake in Thermally Injured Hypermetabolic Patients. Surg. Gynecol. Obstet., 132:881, 1971.
7. Zawacki, B. E., Spitzer, K. W., Mason, A. D., Jr. and Johns, L. A.: Does Increased Evaporative Water Loss Cause Hypermetabolism in Burned Patients? Ann. Surg., 171:236, 1970.

Systemic and Pulmonary Hemodynamic Changes Accompanying Thermal Injury

MORRIS J. ASCH, M.D., LT COL, MC, RICHARD J. FELDMAN, CAPT VC,
HARREL L. WALKER, M.S., F. D. FOLEY, M.D.,
RICHARD L. POPP, M.D.,MAJOR, MC, ARTHUR D. MASON, JR., M.D.,
BASIL A. PRUITT, JR., M.D., COL, MC

From the United States Army Institute of Surgical Research,
Brooke Army Medical Center,
Fort Sam Houston, Texas 78234.

THE PULMONARY response to nonthoracic trauma has been the subject of much discussion and speculation and is not well understood. Congestive atelectasis,[8] fat embolism,[4] and wet lung[10] are some of the names that have been given to the pulmonary problems occurring after trauma. Pulmonary complications are common sequelae of thermal trauma[12] and are significant sources of morbidity and mortality. Many of these complications occur during the first postburn week and are manifested by a poorly understood respiratory distress syndrome, hyperventilation, interstitial pulmonary edema or pneumonitis. This study evaluates the pressure and resistance changes across the pulmonary vascular bed subsequent to thermal trauma and compares these with the concurrent changes in the systemic circulation. The influence of two different fluid resuscitation regimens on circulatory hemodynamics was also evaluated. These studies were performed in unanesthetized dogs.[1] Gross and microscopic observations of the pulmonary vascular bed and electron microscopic studies of the lung were also made on selected dogs.

Methods

Conditioned, adult, mongrel dogs, weighing from 14 to 19 Kg., were used as study subjects. Number 8 French polyethylene feeding tubes were placed percutaneously into the main pulmonary artery, the left atrium, the aortic arch and the terminal superior vena cava and left indwelling (Fig. 1). This was done under fluoroscopic guidance 24 hours prior to burning, using Ketamine anesthesia, occasionally supplemented by a short-acting barbiturate, sodium methohexital. The next day, preburn blood samples for arterial hematocrit, pH, P_{CO_2}, P_{O_2} and mixed venous pH, P_{CO_2}, P_{O_2} and lactic acid were drawn from the aortic and pulmonary artery catheters respectively. Duplicate preburn cardiac output measurements were made along with simultaneous measurements of pulmonary artery, left atrial and systemic arterial pressures. Cardiac output was determined by a dye dilution technic using indocyanine green, the details of which have been reported previously.[11]

Arterial and venous pH, P_{CO_2} and P_{O_2} were measured using the Instrumentation Laboratory blood gas analyzer. Lactic acid was measured by the method of Ellis *et al.*[6] The pulmonary artery and left atrial cannulae were attached to the positive and negative sides of a differential pressure transducer (Sanborn model 268B) to measure the pressure difference across the pulmonary vascular bed. This difference was verified by independently measuring the left atrial and pulmonary arterial pressures on one side of the transducer and subtracting the former from the latter. The aortic cannula was attached to a Statham transducer to measure arterial pressure. Pressures and heart rate were recorded on a Sanborn four-channel recorder (model 964). The positions of all cannulae were confirmed at the time the animals were sacrificed. After these measurements had been performed, all animals were anesthetized for 10 to 20 minutes with sodium methohexital during which time they were shaved and subjected to a 40 to 45% scald burn (12 seconds in water at 99° to 100°C). The area

---

Submitted for publication June 23, 1972.

In conducting the research described in this report the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences—National Research Council.

of the body burned was the entire back and portions of the flanks and upper legs. The animals recovered from anesthesia in 45 to 90 minutes and were randomly divided into four groups of six each: (1) control unburned; (2) burned nonresuscitated; (3) burned and resuscitated with Plasmanate; and (4) burned and resuscitated with Ringer's lactate. The volume of Ringer's lactate or Plasmanate used was 2 cc./kg. body weight per per cent burn (90 ml./Kg.) in the first 24 hours, half being given in the first 8 hours and the remainder in the next 16 hours. Half this volume was administered at a constant rate during the second 24 hours and each dog was allowed to drink one liter of water per day. Measurements of cardiac output, pulmonary arterial, left atrial and systemic arterial pressure were made prior to beginning fluid administration (approximately 90 minutes after burning) and were repeated at 4 and 6 hours postburn and then every 6 hours until the animals were sacrificed at 48 hours. Arterial hematocrit, Pco_2 and Po_2 and mixed venous lactic acid, pH, Pco_2 and Po_2 were measured at the same time intervals. The dogs were sacrificed 48 hours postburn by injecting a bolus of potassium chloride mixed with a suspension of carbon particles into the superior vena cava. A template of the burned area was drawn and the surface area was measured with a planimeter; the per cent of total body surface burned was then calculated. Full thickness cutaneous necrosis was confirmed by histologic examination.

Results

All data were expressed as per cent of preburn value using the preburn determination as 100%. Pulmonary arterial, left atrial and systemic arterial pressures were expressed as mean pressure. The results shown in the graphs reflect mean values plus or minus the standard error of the mean. Resistance data were calculated by dividing mean systemic arterial pressure, or mean pulmonary artery minus mean left atrial pressure, by cardiac output. Systemic central venous pressure was not taken into account in calculating systemic resistance because of its negligible contribution.

Cardiac output. Cardiac output 90 minutes after burning and prior to resuscitation was between 55 and 60% of preburn value in all three groups of burned animals (Fig. 2). A rapid rise was observed thereafter in the Plasmanate resuscitated group so that cardiac output returned to preburn levels between 4 and 6 hours postburn, became significantly higher than preburn levels at 12 hours postburn, and remained so until the end of the 48-hour period. Both the Ringer's lactate resuscitated dogs and the non-resuscitated burned dogs had a much slower return of cardiac output to preburn levels, the former returning to normal at 24 hours and the latter at 30 hours. Ringer's lactate resuscitation produced a supernormal cardiac output 30 hours postburn while the burned dogs that were not resuscitated maintained a cardiac output near preburn levels from 30 to 48 hours postburn. Cardiac output in the non-burned, control dogs remained stable throughout the 48 hours of observation.

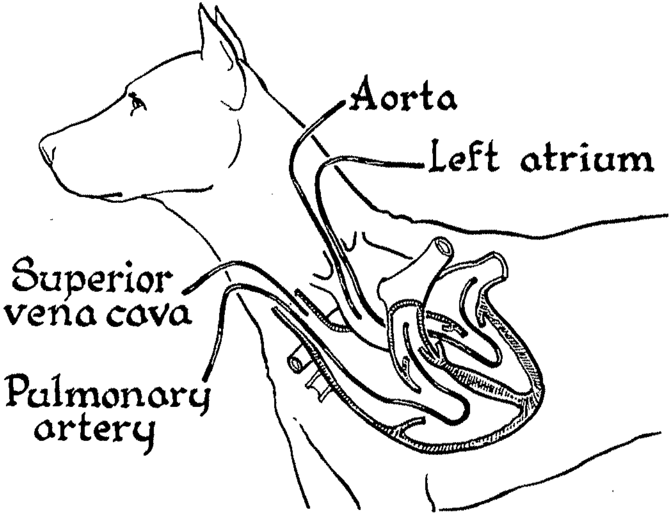


Fig. 1. Diagram illustrating placement of cannulas.

Pulmonary and Systemic Resistance. Pulmonary and systemic resistances were calculated and tabulated separately for each of the three groups of burned dogs. In analyzing these data there was no consistent difference among the three groups. There was, however, a disproportion between pulmonary and systemic resistance changes in all burned dogs (Fig. 3). Mean pulmonary resistance rose to 211% of preburn values 2 hours after injury and gradually fell to preburn levels at 42 hours postburn. Mean systemic resistance rose to 181% 2 hours postburn and returned to preburn values 18 to 24 hours postburn. This difference between pulmonary and systemic resistance change was observed throughout most of the experiment.

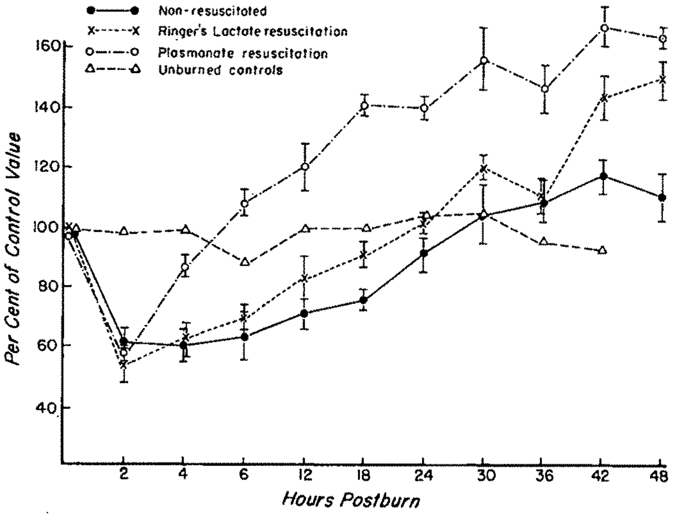


Fig. 2. Change in cardiac output resulting from burn and the influence of Plasmanate and Ringer's lactate fluid resuscitation.

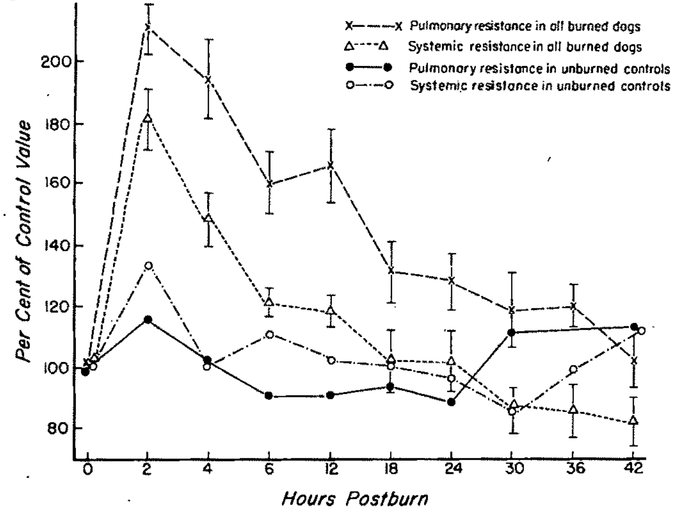


FIG. 3. The effect of thermal injury and resuscitation regimens on pulmonary and systemic vascular resistance compared to changes of resistances in unburned animals.

Pulmonary arterial, left atrial and systemic arterial pressure.

Systemic arterial pressure was relatively stable in all animals. In the resuscitated animals, an elevation of pulmonary arterial pressure occurred with little change of left atrial pressure, increasing the transpulmonary pressure gradient (Fig. 4). In the non-resuscitated animals, both pulmonary arterial and left atrial pressures decreased, with maintenance of a normal transpulmonary pressure gradient despite decreased flow.

pH, P_{CO_2}, P_{O_2} and Lactic Acid Measurements. Analysis of serial arterial and mixed venous pH, P_{CO_2} and P_{O_2} failed to reveal any consistent characteristic change. A decrease in pH and P_{O_2} in the pulmonary arterial blood occurred only occasionally and there was no correlation between these decreases and elevation of pulmonary arterial pressure. Lactic acid was elevated in only a few isolated instances throughout the experiment.

Burn Size. Burn size varied in each group from 37 to 46% of the total body surface. The mean burn size was 41% of the total body surface in the burned nonresuscitated dogs, 40% in the burned, Ringer's lactate resuscitated dogs, and 41% in the burned Plasmanate resuscitated dogs.

The lungs of burned dogs with or without resuscitation appeared more fully perfused than the nonburned. The latter often demonstrated segments of lung that were less dark than adjacent lobules due to variability in distribution of the carbon suspension. Although the lungs of the burned animals appeared darker throughout, the degree of alveolar capillary congestion did not vary by light microscopy among the four groups studied. There was marked variability of carbon distribution between areas of lung sampled and between animals.

Ultrastructural observations revealed alveolar lining cells, granular pneumocytes and pulmonary capillary endothelial cells to be intact in all groups. The interstitial compartment in the thick portion of the alveolo-capillary membrane was generally compact. An isolated focus of interstitial dissection by edema and a few interstitial carbon particles were seen in two resuscitated dogs, the significance of which is uncertain. No edema or hemorrhage was apparent by light microscopy in any of the four groups.

Discussion

The merits of different fluid resuscitation regimens in burn shock have been debated at length. The criteria for an ideal fluid regimen are difficult to delineate and it is apparent that a variety of methods of fluid therapy will permit survival, keep patients out of clinical shock and evoke adequate urine output. Restoration of cardiac output would seem to be an important factor and the early restoration of cardiac output with Plasmanate resuscitation in this experiment is of interest and corroborates the earlier work of Moncrief done in anesthetized dogs.[11] Transcapillary leakage of protein and the inability of others[13] to show an increase in plasma volume with colloid administration seem to rule out a simple volume effect.

There is evidence that a myocardial depressant exists in both burn and hemorrhagic shock.[3,16] It is possible that plasma binding of such a factor by Plasmanate could account for earlier restoration of cardiac output in these animals.

The current report is the first study of pressure and resistance changes in the pulmonary vascular bed in burn shock. The disproportionately greater increase of pulmonary resistance than of systemic resistance is similar to the findings of Cook and Webb[5] in hemorrhagic

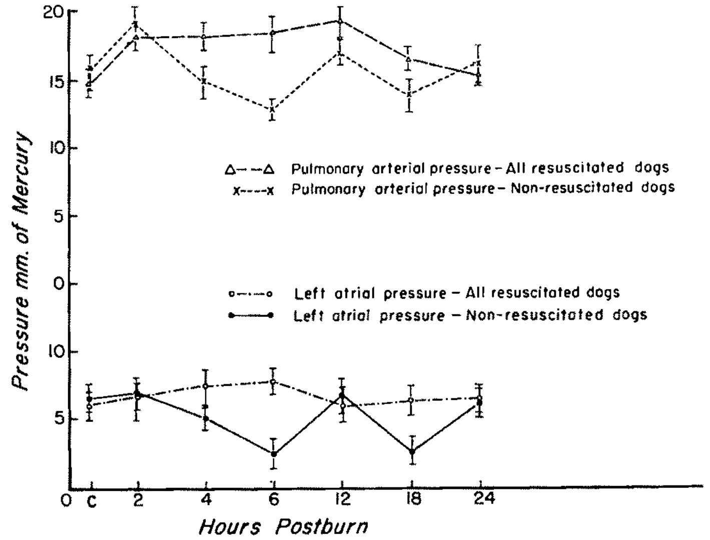


FIG. 4. The effect of thermal injury on pulmonary arterial and left atrial pressure and the difference between no resuscitation and fluid resuscitation.

shock. This may be accounted for by a disproportionate increase in pulmonary arterial vasoconstriction. Decrease in pH and decrease in oxygen tension of pulmonary arterial blood are known to produce pulmonary arterial vasoconstriction[7] but were not factors in the current experiment. A number of vasoactive agents are known to influence the pulmonary circulation[15] and may play a part in the observed elevation of pulmonary arterial pressure. Another possibility, described by West,[17] is that the observed rise in transpulmonary resistance is due to increased mean intra-alveolar and interstitial pressure due to hyperventilation, which occurs following burns[2] and other trauma.[9]

The very occasional lactic acid elevation agrees with a recent clinical study[18] but is at variance with previous work in the anesthetized dog.[11] This is probably explained by better perfusion in the conscious animals.

The gross appearance of the lungs in burned animals is consistent with an increase in pulmonary blood volume as reported in similar studies by Cook.[5] No differences were noted by light microscopy among the four groups studied but small differences would have been obscured by the marked variability in alveolar capillary congestion between areas and also by compression of alveolar capillaries in all groups by intratracheal instillation of fixative under pressure. Light microscopic lung changes following hemorrhagic shock have also been inconsistent.[10]

Ultrastructural pulmonary alterations which have been described in hemorrhagic shock in canine models include interstitial edema and swelling of alveolar epithelium, granular pneumocytes and endothelial lining cells.[14] The interstitial compartment of the lungs in the burned animals, whether resuscitated or not, remained intact for the most part, although rare isolated foci of interstitial edema were found associated with extravasation of particulate carbon in some of the resuscitated animals. In contrast to the ultrastructural cellular changes noted in hemorrhagic shock, no edema or swelling was present in the alveolar epithelium, granular pneumocytes or endothelial lining cells, but this may only reflect a difference in severity or duration of hypovolemia.

Summary

Changes in pulmonary and systemic hemodynamics have been studied in animals with large burns after recovery of consciousness. Increased resistances were observed in both systems and was somewhat more prominent in the pulmonary circulation. Cardiac output responded more promptly to colloid resuscitation than to administration of electrolyte solutions in these animals. Postmortem examination of the lungs revealed only minimal focal interstitial edema and a more uniform perfusion pattern than was observed in unburned control animals.

References

1. Asch, M. J., Mason, A. D., Jr. and Pruitt, B. A., Jr.: Experimental Burn Shock—The Effects of Anesthesia. (In preparation).
2. Asch, M. J., White, M. and Pruitt, B. A., Jr.: Acid Base Changes Associated with topical Sulfamylon Therapy. Ann. Surg., 172:946, 1970.
3. Baxter, C. R., Cook, W. A. and Shires, G. T.: Serum Myocardial Depressant Factor of Burn Shock. Surg. Forum, 17:1, 1966.
4. Collins, J. A., Gordon, W. C., Jr., Hudson, T. L., Irvin, R. W. Jr., Kelly, T. and Hardaway, R. M., III.: Inapparent Hypoxemia in Casualties with Wounded Limbs: Pulmonary Fat Embolism? Ann. Surg., 167:511, 1968.
5. Cook, W. A. and Webb, W. R.: Pulmonary Changes in Hemorrhagic Shock. Surgery, 64:85, 1968.
6. Ellis, J. P., Cain, S. M. and Williams, E. W.: Rapid Accurate Analysis of Blood Lactate. USAF School Aerospace Med. TDR 63-49, 1963.
7. Fishman, A. P.: Dynamics of the Pulmonary Circulation. Handbook of Physiology. Circulation. Washington, D.C., American Physiological Society, 1963, Section II, Vol. 2, Chpt. 48, p. 1167.
8. Jenkins, M. T., Jones, R. F., Wilson, B. W. and Moyer, C. A.: Congestive atelectasis—A Complication of the Intravenous Infusion of Fluids. Ann. Surg., 132:327, 1950.
9. Lyons, J. H., Jr. and Moore, F. D.: Post-traumatic Alkalosis: Incidence in Pathophysiology of Alkalosis in Surgery. Surgery, 60:93, 1966.
10. Martin, A. M., Simmons, R. L. and Heisterkamp, C. A.: Respiratory Insufficiency in Combat Casualties. Pathologic Changes in the Lungs of Patients Dying of Wounds. Ann. Surg., 170:30, 1969.
11. Moncrief, J. A.: The Effects of Various Fluid Regimens and Pharmacologic Agents on the Circulatory Hemodynamics of the Immediate Postburn Period. Ann. Surg., 164:723, 1966.
12. Pruitt, B. A., Jr., Flemma, R. J., DiVincenti, F. J., Foley, F. D. and Mason, A. D., Jr.: Pulmonary Complications in Burn Patients. J. Thorac. Cardiovasc. Surg., 57:7, 1970.
13. Pruitt, B. A., Jr., Mason, A. D., Jr. and Moncrief, J. A.: Hemodynamic Changes in the Early Postburn Patient: The Influence of Fluid Administration and of a Vasodilator (Hydralazine). J. Trauma, 11:36, 1971.
14. Ratliff, N. B., Wilson, J. W., Hackel, D. B. and Martin, A. M., Jr.: The Lung in Hemorrhagic Shock. II. Observations on Alveolar and Vascular Ultrastructure. Am. J. Pathol., 58:353, 1970.
15. Sukhnandan, R. and Thal, A. P.: The Effect of Endotoxin and Vasoactive Agents on Dibenzyline-pretreated Lungs. Surgery, 58:185, 1965.
16. Wangensteen, S. L., DeHoll, J. D., Kieschel, S. F., Martin, J. and Lefer, A. M.: Influence of Hemodialysis on a Myocardial Depressant Factor in Hemorrhagic Shock. Surgery, 67:935, 1970.
17. West, J. B.: Ventilation/Blood Flow and Gas Exchange. Blackwell Sci. Publications. Oxford & Edinborough, 1965.
18. White, M. and Asch, M. J.: The Acid Base Effects of Topical Mafenide Acetate in the Burned Patient. N. Engl. J. Med., 284:1281, 1971.
19. Wilson, J. W., Ratliff, N. B. and Hackel, D. B.: The Lung in Hemorrhagic Shock. I. In vivo Observations of Pulmonary Microcirculation in Cats. Am. J. Pathol., 58:337, 1970.

Sepsis:

A Mechanism for Vasodilatation in the Kidney

FREDRICK RECTOR, M.D., SURESH GOYAL, M.D.,
IRWIN K. ROSENBERG, M.D., CHARLES E. LUCAS, M.D.

From the Robert S. Marx Surgical Laboratories,
Department of Surgery,
Wayne State University School of Medicine,
Detroit, Michigan 48201; and
Detroit General Hospital, Detroit, Michigan

THE SYSTEMIC HEMODYNAMIC effects of severe sepsis reflect a hyperdynamic state characterized by an increased cardiac index, expanded blood volume, widened pulse pressure, expanded extracellular fluid volume and decreased peripheral vascular resistance.[3,20] The renal circulation is classically considered exempt from this hyperdynamic state and responds to sepsis with increased renal vascular resistance and decreased renal flow. Most estimates of renal plasma flow in septic patients, however, have been extrapolated from measurements of para-amino hippurate clearance (C_{PAH}) assuming a constant extraction ratio (E_{PAH}) of 0.91. In view of the many factors such as temperature,[7] liver disease,[8] and acute or chronic fluid loading,[1] which are known to alter E_{PAH}, this assumption must be regarded as highly speculative pending clinical confirmation in septic patients.

Recent clinical[17] and experimental observations[10] of renal function in the presence of sepsis cast some doubt on the concept that the renal circulation is truly exempt from this hyperdynamic state. Clinically,[17] we have identified in a significant number of severely septic patients a syndrome of "inappropriate polyuria" characterized by relatively high urine volumes which tend to deplete the required circulatory volume and lead to hypotension and renal failure if large intravenous fluid replacement is not provided. This syndrome is comparable to that seen in patients receiving phenoxybenzamine. Large volumes of intravenous fluid replacement maintain normal effective circulatory volume as measured by blood pressure and pulse and protect renal function as measured by glomerular filtration rate and effective renal plasma flow. Experimentally, Hermreck and Thal[10] reported an increase in true renal blood flow in dogs with septic hind limbs. This increase in renal blood flow was measured with an electromagnetic flowmeter and correlated directly with a concomitant increase in cardiac output.

The present study was designed to determine: 1) in dogs, the effect of a different septic preparation on renal vascular resistance, and 2) in man, the effect of severe sepsis on renal function and hemodynamics.

Methods

1. *Experimental Studies*

Renal vascular resistance in dogs was measured in an *in situ* isolated canine kidney[13] perfused at a constant rate intermittently with autologous blood, homologous control blood and homologous blood from septic dogs. Laparotomy and left nephrectomy were performed on 16 adult mongrel dogs under pentobarbital anesthesia (25 mg./Kg.) and controlled endotracheal ventilation. The dogs weighed between 15 and 23 Kg. The aorta above and below both renal arteries was dissected free and the intervening lumbar arteries were ligated and divided. The left renal artery was cannulated with a #320 polyethylene catheter for perfusion into the isolated aorto-renal segment (ARS). A second polyethylene catheter was passed retrograde into the ARS via the

---

Supported by the Detroit General Hospital Research Corporation.

Submitted for publication January 28, 1972.

femoral artery and used to monitor continuous ARS pressure. Temporary occlusion with appropriately placed umbilical tapes allowed intermittent isolation of the ARS for purposes of perfusion. The carotid artery was cannulated and used to perfuse the ARS with autologous blood through an occlusive finger pump and to measure systemic pressure.[13] ARS perfusion pressure was maintained slightly above systemic pressure to minimize or eliminate interference from collateral circulation. Flow rates required to maintain this perfusion pressure averaged 103 ml./min. (range: 63–175 ml./min.) All dogs were heparinized (2 mg./Kg.) prior to initiating the perfusion.

The ARS was intermittently perfused with autologous blood from the recipient dog's own carotid artery until reliable baseline measurements were obtained. After equilibration, the ARS was alternately perfused through a three-way stop cock for 20 to 60-second periods with homologous blood obtained from the carotid arteries of both control and septic dogs. Flow rates were kept constant; thus, any change in ARS pressure reflected a change in renal vascular resistance. Following each perfusion with control or septic blood, the ARS was cleared by means of a short-term perfusion with balanced electrolyte solution prior to re-establishing baseline perfusion.

The control dogs received water *ad libitum* from the night prior to operation and cannulation of the carotid artery. The septic dogs were prepared by appendectomy without ligature within 24 hours prior to study. These dogs received no antibiotics but received intravenous balanced electrolyte solution to prevent dehydration. Approximately 60% of the dogs made septic by this method died within 24 hours and were thus not used. Hematocrit and serum osmolalities were monitored in the surviving septic dogs and the control dogs. Only those septic and control dogs with comparable hematocrits (± 3%) and serum osmolalities (± 5%) were included. All dogs with hematocrit levels below 35% and above 45% were excluded. After exclusion of either the dehydrated or hyperosmolar septic animals, a total of 16 ARS preparations were perfused and admissible for statistical evaluation. A total of 25 perfusions from 16 control dogs and 34 perfusions from 16 septic dogs were made into the ARS of 16 recipient animals.

2. *Clinical Studies*

Glomerular filtration rate and effective renal plasma flow were measured by clearances of inulin (C_{IN}) and para-amino hippurate (C_{PAH}) on 34 occasions in 22 severely septic patients with peritonitis due either to hollow viscus perforation or strangulation obstruction. Fifteen of these patients subsequently died and four developed renal failure. Para-amino hippurate extraction ratios (E_{PAH}) were calculated in six of these patients and these measurements were used to calculate true renal blood flow. Measurements of (C_{IN}), (C_{PAH}), and (E_{PAH}) were made during three consecutive 15-minute collection periods after a 45-minute equilibration period, following a bolus injection of inulin and para-amino hippurate calculated to achieve serum levels of 25 mg./100 ml. and 2 mg./100 ml. respectively. Throughout the equilibration and collection periods, a constant infusion of inulin and para-amino hippurate was maintained in order to keep the plasma levels constant. This technic follows the prescribed method of Homer Smith and has been previously reported by us.[17] All studies were made more than 72 hours after the initial operative procedure to minimize or eliminate the effects of anesthesia.

Measurements of (E_{PAH}) in the six severely septic patients were facilitated by placing under direct fluoroscopic control a custom-made #2 wide arc Odman-Ledein type catheter deeply into the right renal vein via a femoral vein. Careful gravity aspiration of blood from these catheters was performed to prevent mixture from inferior vena caval blood. The entire procedure in these six critically ill patients required the careful coordination of both the clinical and renal services along with the intensive care unit nursing personnel and the Department of Radiology. This careful coordination by all involved parties insured optimal patient care throughout the period of renal evaluation. The results of the renal function studies, along with the results of in-depth respiratory and cardiac studies, were used to monitor daily treatment part of which was supervised by the renal unit. All measurements were corrected to 1.73 M^2 surface area and reported as a percentage of the expected norm, which is 125 ± 25 ml./min. for C_{IN} and 650 ± 160 ml./min. for C_{PAH}.[17] Appropriate correlations to the cardiac output determined by cardiogreen dilution technic and total peripheral vascular resistance were made whenever possible.

Results

Experimental Studies

Renal vascular resistance as estimated by the change in ARS pressure while being perfused at a constant flow rate (Average = 103 ml./min.) decreased an average of 34 ± 7.3% SD (69 ± 7.5 ml./min. SD) during 25 perfusions with control blood and 53 ± 8.3% SD (51 ± 8.6 ml./min. SD) during 34 perfusions with septic blood when compared to the baseline perfusion with autologous blood. This decrease in total renal vascular resistance with septic blood over that with control blood in dogs with comparable hematocrits and

TABLE 1. *Effect of Sepsis on Renal Function*

Measurements Studied*	Results
Glomerular Filtration Rate—22 patients C_{IN}(ml./min.)	85 ± 30.3% S.D. (107 ± 38 ml./min. S.D.)
Effective Renal Plasma Flow—22 patients C_{PAH}(ml./min.)	73 ± 29.6 % S. D. (474 ± 192 ml./min. S.D.)
Extraction Ratio Para-amino hippurate in 6 patients E_{PAH} (%)	0.43 Range 0.04 to 0.62
True Renal Plasma Flow in 6 patients C_{PAH}/E_{PAH} in ml./min.	171% Range 51 to 276% (1238 ml./min. Range 364 to 2000 ml./min.)

* Glomerular filtration rate, effective renal plasma flow and true renal plasma flow are expressed as percentage of expected norm corrected to 1.73 M^2 surface area. Actual flow rates are in parentheses.

serum osmolalities was statistically significant ($p = 0.05$).

Clinical Studies

The (C_{IN}) and (C_{PAH}) averaged 85 ± 30.3% SD (107 ± 38 ml./min. SD) and 73 ± 29.6% SD (474 ± 192 ml./min. SD) of the expected norm for the 34 determinations in 22 severely septic patients (Table 1). (E_{PAH}) in the six patients with renal vein samples averaged 0.43 (range = 0.04 to 0.62) compared to an expected normal of 0.91. The two patients with non-oliguric renal failure had an average (C_{IN}) and (C_{PAH}) of 29% (35 ml./min.) and 16% (104 ml./min.) respectively of expected norm. The true renal plasma flow was measured in one of these patients and it was 2000 ml./min. or 276% of expected. Cardiac outputs measured by cardiogreen dilution technique within 36 hours of the renal hemodynamic studies in four patients with (E_{PAH}) measurements averaged 9.0 L/min. reflecting the hyperdynamic state of sepsis. The ratio of true renal blood flow to total cardiac output averaged 21% (range 16% to 26%) in these four patients (Table 2). This rise in true renal blood flow paralleled the increase in cardiac output.

Discussion

The classic concept that sepsis increases renal vascular resistance appears to be an extension of the misconception that sepsis causes increased total peripheral vascular resistance with decreased cardiac output.[11,15,16] This interpretation of the systemic and renal hemodynamic effects of sepsis is based primarily on animal studies where various artificial preparations were used to mimic clinical sepsis. Unfortunately, clinical sepsis is not a pure syndrome that can be reproduced by infusion of endotoxin or other bacterial products but is a complex physiologic response to a multiplicity of offending stimuli released from various bacteria with their appropriate toxins and several factors which have not yet been identified. The systemic vasodilatory effects of sepsis became documented only when investigation shifted from the experimental laboratory to the intensive care unit. These systemic hemodynamic studies were facilitated by the accurate measurements of true cardiac output which can be obtained by using the cardiogreen dilution technic. Accurate measurements of true renal blood flow have in the past been hampered by the difficulties inherent in obtaining uncontaminated renal vein samples when measuring para-amino hippurate clearance. This led to the frequent use of para-amino hippurate clear-

TABLE 2. *Sepsis and Renal Hemodynamics—Parameters Studied**

Patients	GFR (C_{IN})	ERPF (C_{PAH})	Extraction Ratio (E_{PAH})	TRPF ($C_{PAH}/(E_{PAH})$	Renal Blood Flow Cardiac Output
1.	12% †(15 ml./min.)	12% (80 ml./min.)	4%	276% (2000 ml./min.)	19%
2.	136% (169 ml./min.)	135% (883 ml./min.)	62%	196% (1424 ml./min.)	23%
3.	97% (121 ml./min.)	106% (687 ml./min.)	48%	198% (1431 ml./min.)	26%
4.	114% (149 ml./min.)	79% (515 ml./min.)	45%	158% (1144 ml./min.)	—
5.	76% (95 ml./min.)	69% (448 ml./min.)	42%	147% (1066 ml./min.)	16%
6.	86% (107 ml./min.)	31% (207 ml./min.)	56%	51% (364 ml./min.)	—
Average	87% (109 ml./min.)	72% (470 ml./min.)	0.43	171% (1238 ml./min.)	21%

* GFR, ERPF and TRPF measurements are corrected to % of expected norm per 1.73 M^2.
† Actual flow rates are in parentheses.

ance as a measurement of renal plasma flow assuming a constant extraction ratio of 0.91. It is apparent from the present study that this assumption is invalid and previous clinical measurements of renal blood flow using this technic must be discounted. Clearance of para-amino hippurate must be regarded as only a measurement of effective renal plasma flow by which one measures plasma perfusing functioning nephrons.

Hermreck and Thal[10] were the first to document a decrease in renal vascular resistance in septic animals. They used an electromagnetic flowmeter to measure flow through the renal artery in dogs with septic limbs. Using the same animal model for sepsis[18] we found a significant decrease in effective renal plasma flow but no decrease in true renal plasma flow. The extraction of para-amino hippurate in these animals was significantly reduced in comparison to control dogs. Thal postulated that increased renal blood flow in this preparation was due to the release of vasoactive agents such as endogenous pyrogens.[5] This concept is supported by the decrease in renal vascular resistance seen in the isolated aorto-renal segment when being perfused at a constant flow with blood from a septic animal. Clinical support of this concept has been limited previously to the study of renal hemodynamics following pyrogen,[4,12] or bradykinin[6] administration in human volunteers. These patients developed renal hyperemia with increased true renal blood flow and sodium excretion. The present study demonstrates that the kidney does share in this hyperdynamic state in critically ill septic patients.

The mechanism whereby renal vascular resistance is decreased in septic patients is uncertain. The hyperdynamic state seen clinically with massive sepsis is not accompanied by a similar increase in oxygen consumption,[2,20] so that systemic shunting seems likely. Such shunting is either physiologic whereby red blood cells passing through capillaries of septic areas are not releasing oxygen, or else anatomic in which pre-capillary arteriovenous communications allow the blood to bypass the cells. A similar phenomenon apparently is operative within the kidney. This may result from a redistribution of blood flow decreasing cortical flow while the medullary flow increases.[14] Such a redistribution could result in selected tubules exceeding their transport maximum for secreting para-amino hippurate. The effect of specific factors such as drugs, acidosis, or fever, upon the efficiency of the transport mechanism of these perfused tubules, however, is unknown. Alternatively, the blood may be perfusing the tubules evenly but the cells may not transport the para-amino hippurate as a result of injury to the transport mechanism. Regardless of which mechanism is active, extraction of para-amino hippurate is decreased while true renal blood flow increases in proportion to the increase in cardiac output.

The hyperdynamic renal circulation may explain the "inappropriate polyuria" which has been observed in many of these patients.[17] These patients may excrete from 200 to 500 cc. urine per hour at the expense of the circulatory volume resulting in hypotension if intravenous fluid replacement is not provided. This polyuria may reflect the increased solute[4] and sodium excretion[4] seen with renal hyperemia in man following pyrogen administration. Alternatively, pre-glomerular arterial venous shunting may increase renal venuole pressure sufficiently to impair sodium reabsorption. Certainly the anatomic and physiologic mechanisms of renal hyperemia in sepsis needs to be further clarified. Currently we are exploring the role of osmolar clearance, sodium reabsorption and renal venous pressure in comparable septic patients. Pending better understanding of renal hyperemia in sepsis, clinicians should anticipate inappropriately high urine excretion in septic patients. Fluid and electrolyte replacement in such patients is facilitated by close monitoring of urinary sodium concentration which, if inordinately low, reflects effective hypovolemia even when actual measurements of blood volume and central venous pressure are elevated.

Summary

The effects of sepsis on renal hemodynamics were studied: 1) Experimentally in dogs, by constant flow perfusions of both control and septic blood into an *in situ* isolated aorto-renal segment (ARS) in which a change in pressure reflects a change in renal vascular resistance (RVR) and 2) Clinically, by serial measurements of para-amino hippurate (ERPF) and Inulin clearance (GFR) in 22 septic patients and para-amino hippurate extraction ratio (E_{PAH}) in six critical septic patients.

Experimentally, RVR in the ARS decreased an average of 34% with control blood and 53% with septic blood. Clinically, GFR and ERPF averaged 85% and 73% of expected norm in 22 patients and E_{PAH} averaged 0.43 in six patients. Total renal blood flow averaged 171% of expected norm in six patients and 21% of cardiac output in four patients. The possible etiology and clinical implications of this renal hyperemia in septic patients are discussed.

References

1. Biglieri, E. G. and Forsham, P. H.: Studies on the Expanded Extracellular Fluid and the Responses to Various Stimuli in Primary Aldosteronism. Am. J. Med., 30:564, 1961.
2. Clowes, Jr., G. H. A., Vucinic, M. and Weidner, M. G.: Circulatory and Metabolic Alterations Associated with Survival or Death in Peritonitis. Ann. Surg., 163:866, 1966.

3. Cohn, J. D., Greenspan, M., Goldstein, C. R., Gudwin, A. L., Siegel, J. H. and Del Guercio, L. R. M.: Arteriovenous Shunting in High Cardiac Output Shock Syndromes. Surg. Gynecol. Obstet., **127**:282, 1968.
4. Combos, E. A., Lee, T. H., Solinas, J. and Mitrovic, M.: Renal Response to Pyrogen in Normotensive and Hypertensive Man. Circulation, **36**:555, 1967.
5. Cooper, K. E.: Mechanisms of Action of Pyrogens. Fed. Proc., **22**:721, 1963.
6. Gill, Jr., J. R., Melmon, K. L., Gillespie, Jr., L. and Bartter, F. C.: Bradykinin and Renal Function in Normal Man: Effects of Adrenergic Blockade. Am. J. Physiol., **209**:844, 1965.
7. Gillenwater, J. Y., Frohlick, E. D. and Keller, A. D.: Differential Effects of Heat on Splenic and Renal Vascular Beds. Am. J. Physiol., **207**:133, 1964.
8. Gordon, M. E.: The Acute Effects of Abdominal Paracentesis in Laennec's Cirrhosis upon Changes in Electrolytes and Water, Renal Function and Hemodynamics. Am. J. Gastroenterol., **33**:15, 1960.
9. Hahn, H. H., Char, D. C., Postel, W. B. and Wood, W. B.: Studies on the Pathogenesis of Fever XV. The Production of Endogenous Pyrogen by Peritoneal Macrophages. J. Exptl. Med., **126**:385, 1967.
10. Hermreck, A. S. and Thal, A. P.: Mechanisms for the High Circulatory Requirements in Sepsis and Septic Shock. Ann. Surg., **170**:677, 1969.
11. Hinshaw, L. B., Emerson, Jr., T. E. and Reins, D. A.: Cardiovascular Responses of the Primate in Endotoxin Shock. Am. J. Physiol., **210**:335, 1966.
12. Lathem, W.: The Urinary Excretion of Sodium and Potassium During the Pyrogenic Reaction in Man. J. Clin. Invest., **35**:947, 1956.
13. Lucas, C. E. and Read, R. C.: Red Cell Crenation and the Renal Hemodynamic Effect of Mannitol. Surgery, **59**:408, 1966.
14. McNay, J. L. and Abe, Y.: Redistribution of Cortical Blood Flow During Renal Vasodilatation in Dogs. Circ. Res., **27**: 1023, 1970.
15. Priano, L. L., Wilson, R. D. and Traber, D. L.: Cardiorespiratory Alterations in Unanesthetized Dogs Due to Gram-negative Bacterial Endotoxin. Am. J. Physiol., **220**: 705, 1971.
16. Reddin, J. L., Starzecki, B. and Spink, W. W.: Comparative Hemodynamic and Humoral Responses of Puppies and Adult Dogs to Endotoxin. Am. J. Physiol., **210**:540, 1966.
17. Rosenberg, I. K., Gupta, S. L., Lucas, C. E., Khan, A. A. and Rosenberg, B. F.: Renal Insufficiency After Sepsis and Trauma: A Prospective Functional and Ultrastructual Analysis. Arch. Surg., **103**:175, 1971.
18. Sankaran, S., Rosenberg, I. K. and Lucas, C. E.: Unpublished data.
19. Webster, M. E. and Gilmore, J. P.: Influence of Kallidin-10 on Renal Function. Am. J. Physiol., **206**:714, 1964.
20. Wilson, R. F., Thal, A. P., Kindling, P. H., Grifka, T. and Ackerman, E.: Hemodynamic Measurements in Septic Shock. Arch. Surg., **91**:121, 1965.

All of these mammals, except one, can synthesize vitamin C.

Man cannot.

Homo sapiens can neither synthesize vitamin C nor store most of the water soluble vitamins. They should be replenished every day.

Normally, man accomplishes this in his daily diet. But under conditions of illness, stress, in convalescence or following surgery, vitamin stores may be depleted or metabolic demands increased.

In such cases, Surbex-T may be indicated. Each tablet provides 500 mg. of vitamin C plus high potency B-complex.

Where nutritional status must be preserved, Surbex-T can help restore what the body can *not* store.

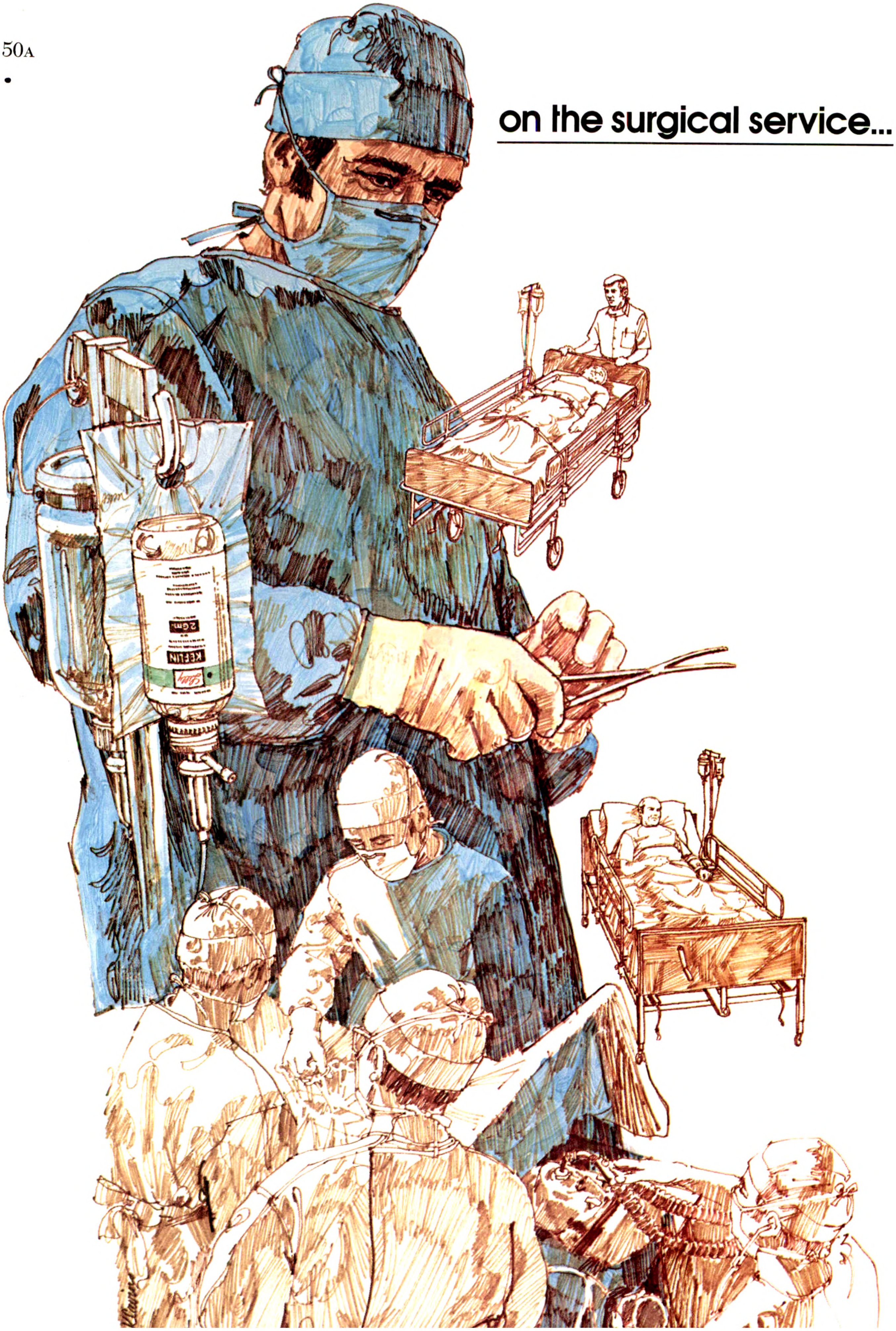
306399R

SURBEX-T® 500 mg. of Vitamin C with High Potency B-Complex

Restores what the body cannot effectively store

ABBOTT

on the surgical service...



more than 10 years of clinical experience★

Keflin® I.V.

sodium cephalothin

2 Gm.* in 100-ml. ampoule

for sepsis and pneumonias†

Over the years, Keflin has been, and continues to be, a logical choice of surgeons for the treatment of sepsis and pneumonias with or without septicemia or shock when due to susceptible strains of *Klebsiella, Escherichia coli,* and *Proteus mirabilis. Pseudomonas* is resistant; many strains of enterococci, such as *Streptococcus faecalis,* are relatively resistant. Keflin is contraindicated in persons who have shown hypersensitivity to cephalosporins and should be used with great caution in patients allergic to penicillin.

The prompt administration of Keflin has proved to be useful in the hospital for the treatment of sepsis, particularly if shock is present or impending. Furthermore, it may even be given to:

- patients with impaired renal function, at reduced dosage
- patients with low host resistance
- those with coexisting complications, such as malnutrition, trauma, and malignancy

Since the introduction of Keflin, the susceptibilities of commonly encountered organisms, as measured by in-vitro methods, have not changed significantly.

*equivalent to cephalothin

†due to susceptible organisms

★Keflin was made available for clinical investigation early in 1962 and was marketed on September 4, 1964.

300560

Lilly

Please turn page for prescribing information.

Description: Keflin® (sodium cephalothin, Lilly) is a semisynthetic cephalosporin antibiotic for parenteral use. It is the sodium salt of 7-(thiophene-2-acetamido) cephalosporanic acid. The sodium content is 55 mg. per Gm. of cephalothin.

Actions: *Microbiology*—The bactericidal action of cephalothin results from inhibition of cell-wall synthesis. In-vitro and in-vivo activity has been demonstrated against strains of the following micro-organisms:

- *Staphylococcus aureus* (penicillin-sensitive and penicillinase-producing)
- Beta-hemolytic and other streptococci (many strains of enterococci, e.g., *Streptococcus faecalis,* are relatively resistant)
- Pneumococci
- Clostridia
- *Hemophilus influenzae*
- *Neisseria gonorrhoeae*
- *Escherichia coli* and other coliform bacteria
- *Klebsiella-Enterobacter* sp.
- *Proteus*
- *Salmonella* sp.
- *Shigella* sp.

Indications: Keflin is indicated in the treatment of serious infections of the respiratory tract, genito-urinary tract, soft tissue and skin, gastro-intestinal tract, bones and joints, bloodstream, and cardiovascular system due to susceptible organisms. Also, it has been effective in cases of peritonitis, septic abortion, and staphylococcal and pneumococcal meningitis. Effectiveness has not been established in other types of meningeal infection.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Keflin.

Contraindication: Keflin is contraindicated in persons who have shown hypersensitivity to cephalosporin antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN C DERIVATIVES SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS. INSTANCES OF PATIENTS WHO HAVE HAD SEVERE REACTIONS TO BOTH DRUGS, INCLUDING DEATH FROM ANAPHYLAXIS, HAVE BEEN REPORTED.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exception should be made with regard to Keflin.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions: Patients should be followed carefully so that any side-effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to Keflin occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine, antihistamines, pressor amines, or corticosteroids).

When Keflin is administered to patients with transient or persistent reduction of urinary output due to impaired renal function, the total daily dose should be reduced. Careful clinical observation and laboratory studies should be made, because higher and more prolonged systemic antibiotic concentrations can occur (see Administration and Dosage below).

When intravenous doses of cephalothin larger than 6 Gm. daily are given by infusion for periods longer than three days, they may be associated with thrombophlebitis, and the veins may have to be alternated. The addition of 10 to 25 mg. of hydrocortisone to intravenous solutions containing 4 to 6 Gm. of cephalothin may reduce the incidence of thrombophlebitis. The use of small I.V. needles in the larger available veins may be preferred.

Prolonged use of Keflin® (sodium cephalothin, Lilly) may result in the overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest® tablets but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: *Hypersensitivity*—Maculopapular rash, urticaria, reactions resembling serum sickness, and anaphylaxis have been reported. Eosinophilia and drug fever have been observed to be associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—Neutropenia and hemolytic anemia have been reported. Some individuals, particularly those with azotemia, have developed positive direct Coombs tests during cephalothin therapy.

Liver—Transient rise in SGOT has been noted.

Kidney—Rise in BUN has been observed; however, some patients with elevated BUN at the beginning of cephalothin therapy have had values return to normal during treatment.

Local Reactions—Pain, induration, tenderness, and elevation of temperature have been reported following repeated intramuscular injections. Thrombophlebitis has occurred and is usually associated with daily doses of over 6 Gm. given by infusion for more than three days.

Administration and Dosage: *In adults,* the usual dosage range is 500 mg. to 1 Gm. of cephalothin every four to six hours. A dosage of 500 mg. every six hours is adequate in uncomplicated pneumonia, furunculosis with cellulitis, and most urinary tract infections. In severe infections, this may be increased by giving the injections every four hours or, when the desired response is not obtained, by raising the dose to 1 Gm. In life-threatening infections, doses up to 2 Gm. every four hours may be required.

In infants and children, the dosage should be proportionately less in accordance with age, weight, and severity of infection. Daily administration of 50 mg. per Kg. (40 to 80 mg. per Kg. or 20 to 40 mg. per pound) in divided doses has been found effective for most infections susceptible to Keflin.

For additional information regarding dosage and administration, see package literature.

How Supplied: Ampoules Keflin® (Sterile Sodium Cephalothin, U.S.P.), equivalent to 1 Gm. cephalothin, 10-ml. size, rubber-stoppered, in packages of 1 and eggcrate cartons of 25; equivalent to 2 Gm. cephalothin, 100-ml. size, rubber-stoppered, in packages of 1 and eggcrate cartons of 10; equivalent to 4 Gm. cephalothin, 50-ml. size, rubber-stoppered, in packages of 1 and eggcrate cartons of 10. [013173]

on the surgical service...

Keflin® I.V.
sodium cephalothin
2 Gm.* in 100-ml. ampoule
*equivalent to cephalothin

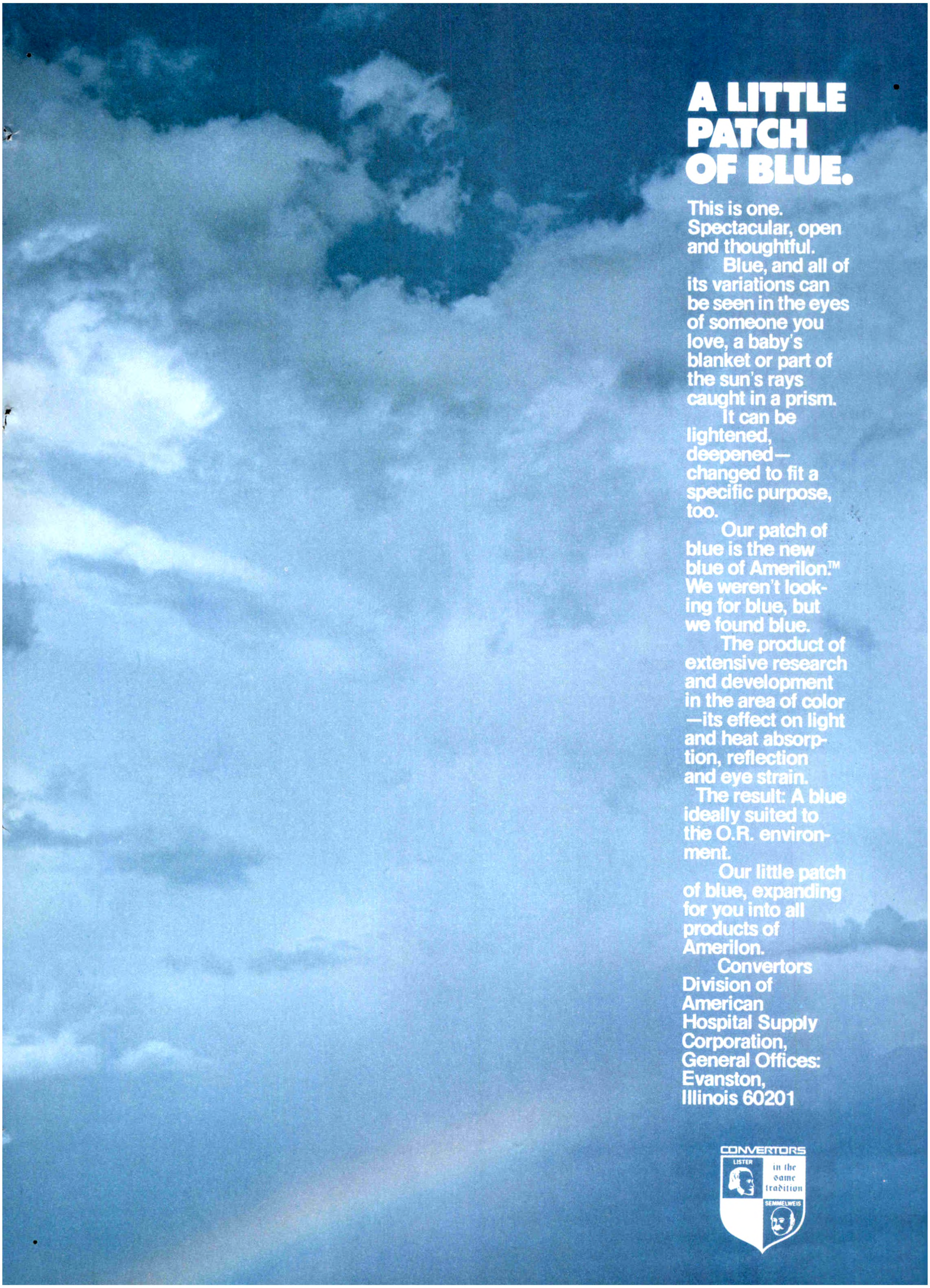
10 years of
clinical
experience

Additional information
available to the
profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

Lilly

300767



A LITTLE PATCH OF BLUE.

This is one. Spectacular, open and thoughtful.

Blue, and all of its variations can be seen in the eyes of someone you love, a baby's blanket or part of the sun's rays caught in a prism.

It can be lightened, deepened—changed to fit a specific purpose, too.

Our patch of blue is the new blue of Amerilon.™ We weren't looking for blue, but we found blue.

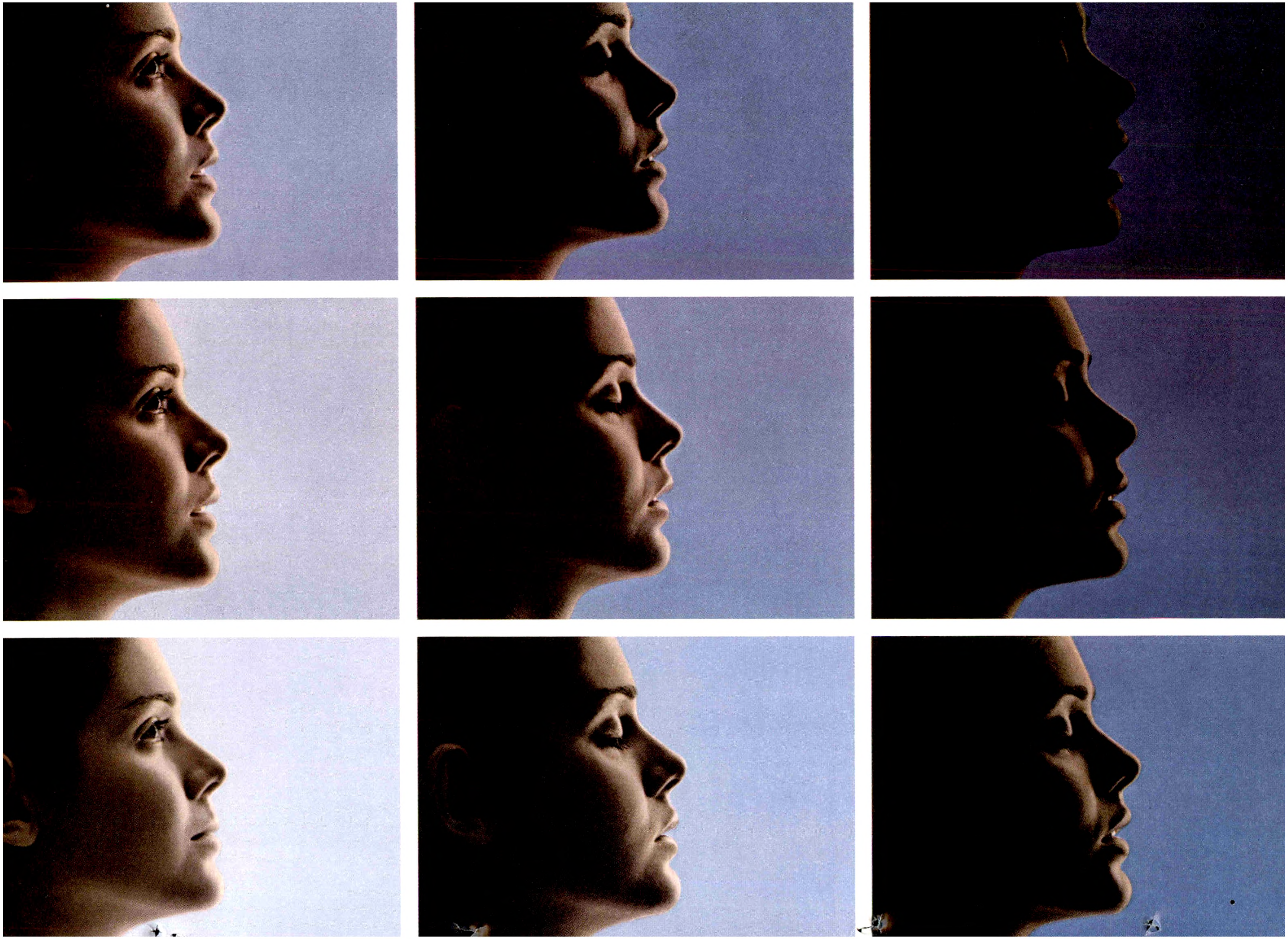
The product of extensive research and development in the area of color—its effect on light and heat absorption, reflection and eye strain.

The result: A blue ideally suited to the O.R. environment.

Our little patch of blue, expanding for you into all products of Amerilon.

Convertors
Division of
American
Hospital Supply
Corporation,
General Offices:
Evanston,
Illinois 60201

CONVERTORS
LISTER
in the same tradition
SEMMELWEIS



Three ways to minimize emergence reactions when you use Kētalar®

(Ketamine HCl)

Let's face it: nearly every anesthesiologist knows by now that Ketalar is an unusually effective general anesthetic or induction agent, with a wide margin of safety. Many view it, in fact, as a major advance in the treatment of such high-risk patients as the very young and the very old... burn cases... accident victims... and those suffering from respiratory disorders such as emphysema.

And nearly every anesthesiologist also knows from the literature (or his own personal experience) that some patients have experienced unpleasant emergence reactions following the administration of Ketalar.

What is perhaps less known is that a combination of patient selection, addition of certain drugs, and the lessening of external stimuli has proved effective in reducing the incidence and severity of emergence reactions. These techniques are easy to apply and, according to many clinical investigators, are remarkably useful.

1. Presurgical medication

High on the list of methods of reducing emergence reactions are certain drugs used preoperatively. These reactions can often be prevented by administering:

Droperidol, 0.1 mg/kg, IM, 30 minutes before anesthesia.

2. Postsurgical medication

After surgery, emergence reactions can often be aborted or prevented entirely by administering one of the following:

Droperidol, 0.07 to 0.1 mg/kg, IV
Diazepam, 0.1 to 0.3 mg/kg, IV
A subanesthetic dose of an ultrashort-acting barbiturate.

3. Avoid tactile and auditory stimuli whenever possible

The incidence of emergence reactions following Ketalar anesthesia appears to be profoundly affected by external auditory and tactile stimuli. Ideally, the patient should be engaged in calm, noncontroversial conversation (on a single subject, if possible) before surgery; afterward, he should be permitted to emerge from anesthesia with minimal auditory, visual, and tactile stimuli.

Will the three preventive techniques discussed here—patient selection, drugs, and ambience—obviate all emergence reactions following Ketalar anesthesia? No, but they will significantly reduce the incidence and severity of those reactions.

Any assessment of Ketalar, however, should take into account its many important advantages—especially for the high-risk patient, where efficacy and a wide margin of safety have made it increasingly valuable to today's anesthesiologists. As more and more are discovering every day.

See next page for prescribing information.

advancement in
anesthesiology

Kētalar
(Ketamine HCl)
Parke-Davis

advancement in anesthesiology

Ketalar®
(KetamineHCl)

KETALAR (Ketamine Hydrochloride)

SPECIAL NOTE: EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12 PER CENT OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT DREAM-LIKE STATES, VIVID IMAGERY, HALLUCINATIONS AND EMERGENCE DELIRIUM. IN SOME CASES THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY LASTS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY.

THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS. IN ADDITION, THE USE OF A SMALL HYPNOTIC-DOSE OF A SHORT-ACTING OR ULTRASHORT-ACTING BARBITURATE OR OTHER AGENT SUCH AS DIAZEPAM MAY BE REQUIRED TO TERMINATE A SEVERE EMERGENCE REACTION. CERTAIN DRUGS SUCH AS DROPERIDOL OR DIAZEPAM INTRAMUSCULARLY HAVE ALSO BEEN USED IN AN ATTEMPT TO REDUCE THE INCIDENCE OF EMERGENCE REACTIONS: SUFFICIENT DATA HAVE NOT YET BEEN ACCUMULATED TO CONSTITUTE THOROUGH DOCUMENTATION. THE INCIDENCE OF EMERGENCE REACTIONS IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

INDICATIONS: Ketalar is recommended: 1. as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketalar is best suited for short procedures but it can be used, with additional doses, for longer procedures. 2. for the induction of anesthesia prior to the administration of other general anesthetic agents. 3. to supplement low-potency agents, such as nitrous oxide.

See package insert for full prescribing information.

CONTRAINDICATIONS: Ketalar is contraindicated in persons in whom a significant elevation of blood pressure would constitute a serious hazard and those who have shown hypersensitivity to the drug.

WARNINGS: Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation. Barbiturates and Ketalar *should not* be injected from the same syringe. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar. Postoperative confusional states may occur during the recovery period. Respiratory depression may occur with over-dosage or too rapid a rate of administration of Ketalar in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

USAGE IN PREGNANCY: Since the safe use in pregnancy, including obstetrics, has not been established, such use is not recommended.

PRECAUTIONS: Because pharyngeal and laryngeal reflexes are usually active, Ketalar should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances. Resuscitative equipment should be ready for use. *The incidence of emergence reactions may be reduced* if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note). The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response. In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

ADVERSE REACTIONS: *Cardiovascular:* Blood pressure and pulse rate are frequently elevated following administration of Ketalar. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketalar. Laryngospasms and other forms of airway obstruction have occurred during Ketalar anesthesia.

Eye: Diplopia and nystagmus have been noted following Ketalar administration. It also may cause a slight elevation in intraocular pressure measurement.

Psychological: (See Special Note).

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures.

Gastrointestinal: Anorexia, nausea or vomiting have been observed; however this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness.

General: Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

HOW SUPPLIED: Ketalar solutions containing the hydrochloride in concentrations equivalent to ketamine base are available in 5, 10, 20, and 50 ml. vials. These vials contain 100, 50, 10, and 10 mg./ml., respectively. Each vial is supplied individually and in cartons of 10.

LG

PARKE-DAVIS

PARKE, DAVIS & COMPANY Detroit, Michigan 48232

PD-JA-1095-1-P (7-73)

INDEX TO ADVERTISERS

PHARMACEUTICAL SUPPLIES

Abbott Laboratories
  Surbex T 49A

Ayerst Laboratories
  Fluothane 18A,19A,20A

Burroughs Wellcome & Company
  Empirin . . . . 15A,Cover IV

Eaton Laboratories
  Vivonex HN 2A

Flint Laboratories
  Travase 47A,48A

Knoll Pharmaceuticals
  Dilaudid 9A
  Santyl 23A,24A

Eli Lilly & Company
  Darvon Comp. 3A
  Keflex . . . . 58A,Cover III
  Keflin 50A,51A,52A
  Loridine 16A

McGaw Laboratories
  Freamine 30A,31A

Mead Johnson
  Mucomyst 12A,13A

Parke-Davis Company
  Ketalar 54A,55A,56A

Purdue Frederick Company
  Senokot 4A

Reed & Carnrick
  Laxsil 21A

A. H. Robins Co. 28A,29A

Roche Laboratories
  Berocca 27A
  Valium 60A,61A,62A

Schering Corporation
  Garamycin 34A,35A

SUPPLIES AND EQUIPMENT

Convertors
  Amerilon 53A

Ethicon, Inc.
  Control Release Needles 41A-44A

C. B. Fleet Co., Inc. 38A

Fuller Laboratories
  Tucks 45A

Parke-Davis Company
  Elase 32A,33A
  Support Hose 11A
  Surgical Instruments . . . . Cover II

Purdue Frederick Company
  Betadine Disposables 1A
  Betadine Microbicides 36A,37A

Richards Manufacturing Co.
  Fiber Bundles 7A

Seamless 14A

Sparta Instrument Corporation 17A

Edward Weck & Co., Inc.
  Hemoclips 22A

MISCELLANEOUS

Franklin H. Martin Memorial Foundation . . . 39A

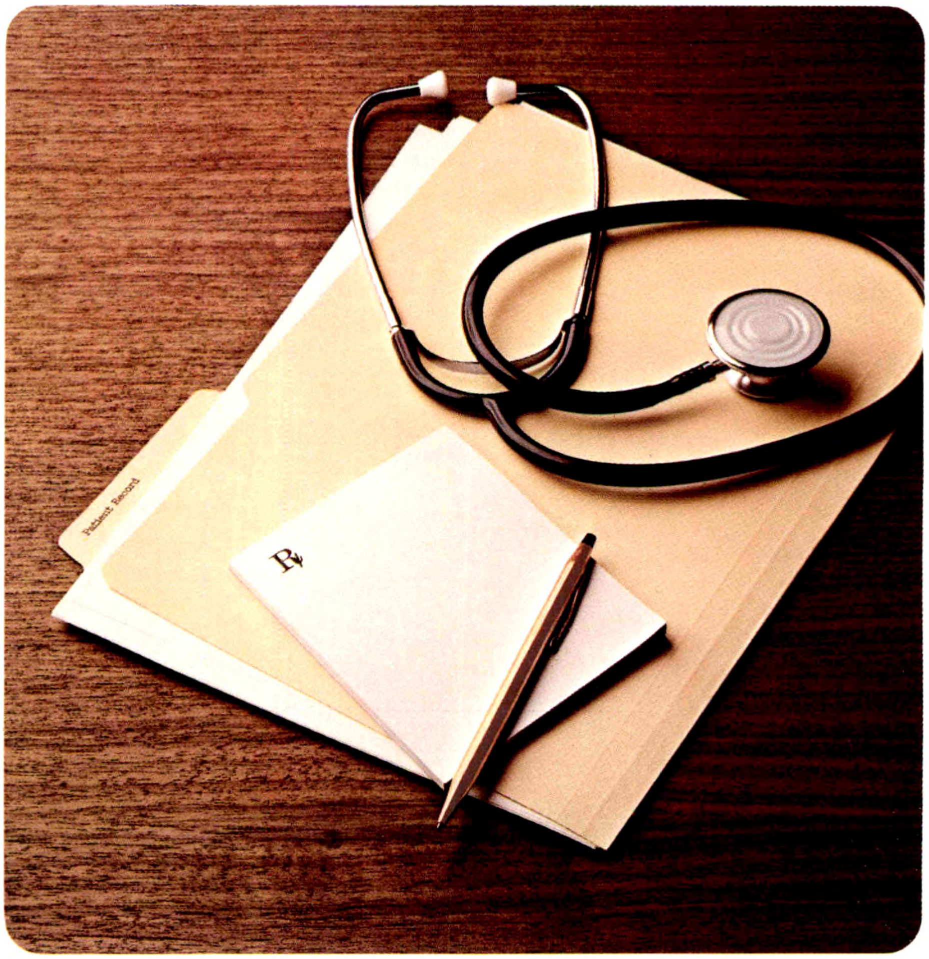
Grune & Stratton, Inc. 46A

J. B. Lippincott Co. 26A,31A,40A,45A

W. B. Saunders Company 25A

so important
in the hospital

just as useful
in the office



Clinical trial experience

Clinical trials establish the usefulness of Keflex in both the hospital and the office.

Effective in an important range of infections

Keflex is appropriate in a variety of infections that are treated in office practice:

Respiratory infections, such as bronchitis, pneumonia, and bronchopneumonia, due to susceptible strains of *Diplococcus pneumoniae*

Urinary tract infections caused by susceptible strains of *Escherichia coli*, *Proteus mirabilis*, or *Klebsiella* sp.

Skin and soft-tissue infections due to susceptible strains of staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains

High blood levels, bactericidal activity in vitro

With Keflex, peak serum levels are reached in one hour. For example, following a single 500-mg. dose, average peak serum levels are approximately 18 mcg. per ml.

In addition, in-vitro studies demonstrate that the cephalosporins exhibit bactericidal activity (by inhibition of cell-wall synthesis) against susceptible organisms. (The in-vivo mechanism cannot be determined, of course, because no method exists for clinical demonstration.)

Acid stable, rapidly absorbed

Because Keflex is acid stable, it may be given without regard to meals. Furthermore, it is rapidly absorbed after oral administration.

A good choice in the office

There are a host of reasons for prescribing Keflex with confidence in the office. That's why it is so often a good first choice when indicated.

Note: Keflex is contraindicated in patients with known allergy to cephalosporins and should be used with great caution in patients allergic to penicillin. The most frequent side-effects are gastro-intestinal.

Prescribing Information

Description: Keflex is a semisynthetic cephalosporin antibiotic intended for oral administration. It is 7-(D-α-amino-α-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid, monohydrate.

Actions: *Human Pharmacology*—Keflex is acid stable and may be given without regard to meals. It is rapidly absorbed after oral administration. Following doses of 250 and 500 mg., average peak serum levels of approximately 9 to 18 mcg. per ml. respectively were obtained at one hour. Measurable levels were present six hours after administration. Over 90 percent of the drug is excreted unchanged in the urine within eight hours. Peak urine concentrations are approximately 1,000 mcg. per ml. during this period following a 250-mg. dose.

Microbiology—In-vitro tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Keflex is active against the following organisms in vitro:

Beta-hemolytic streptococci/Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains/*Diplococcus pneumoniae*/*Escherichia coli*/*Proteus mirabilis*/*Klebsiella* sp.

Note—Most strains of enterococci (*Streptococcus faecalis*) and a few strains of staphylococci are resistant to Keflex. It is not active against most strains of *Enterobacter* sp., *Pr. morganii*, and *Pr. vulgaris*. It has no activity against *Pseudomonas* or *Herellea* species. When tested by in-vitro methods, staphylococci exhibit cross-resistance between Keflex and methicillin-type antibiotics.

Indications: Keflex is indicated for the treatment of the following infections when caused by susceptible strains of the designated micro-organisms:

Respiratory tract infections caused by *D. pneumoniae* and group A beta-hemolytic streptococci (Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Keflex is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of Keflex in the subsequent prevention of rheumatic fever are not available at present.)

Skin and soft-tissue infections caused by staphylococci and/or streptococci

Genito-urinary tract infections, including acute prostatitis, caused by *Esch. coli*, *Pr. mirabilis*, and *Klebsiella* sp.

Note—Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

Contraindication: Keflex is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORIN C DERIVATIVES SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exception should be made with regard to Keflex.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions: Patients should be followed carefully so that any side-effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to Keflex occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine, antihistamines, pressor amines, or corticosteroids).

Prolonged use of Keflex may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

Keflex should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

As a result of administration of Keflex, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: *Gastro-Intestinal*—The most frequent side-effect has been diarrhea. It was very rarely severe enough to warrant cessation of therapy. Nausea, vomiting, dyspepsia, and abdominal pain have also occurred.

Hypersensitivity—Allergies (in the form of rash, urticaria, and angioedema) have been observed. These reactions usually subsided upon discontinuation of the drug.

Other reactions have included genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, and headache. Eosinophilia, neutropenia, and slight elevations in SGOT and SGPT have been reported.

Administration and Dosage: Keflex is administered orally. The adult dosage ranges from 1 to 4 Gm. daily in divided doses. The usual adult dose is 250 mg. every six hours. For more severe infections or those caused by less susceptible organisms, larger doses may be needed. If daily doses of Keflex greater than 4 Gm. are required, parenteral cephalosporins, in appropriate doses, should be considered.

The recommended daily dosage for children is 25 to 50 mg. per Kg. divided into four doses.

In severe infections, the dosage may be doubled.

In the treatment of beta-hemolytic streptococcal infections, a therapeutic dosage of Keflex should be administered for at least ten days.

How Supplied: Pulvules® Keflex® (cephalexin monohydrate, Lilly), equivalent to 250 or 500 mg. cephalexin, in bottles of 24 and 100 and in Identi-Dose® (unit dose medication, Lilly) in boxes of 100.

Keflex, for Oral Suspension, equivalent to 125 mg. cephalexin per 5-ml. teaspoonful, in 60 and 100-ml.-size packages and in Identi-Dose in packages of 100.

Keflex, for Pediatric Drops, equivalent to 100 mg. cephalexin per ml. (5 mg. per drop), in 10-ml.-size packages, with dropper calibrated at 25 and 50 mg.

[121172]

Keflex® 250-mg. Pulvules®
cephalexin monohydrate

so often a good first choice

Additional information available to the profession on request.
Eli Lilly and Company • Indianapolis, Indiana 46206

Lilly

300941

Healing nicely, but it still HURTS

HERE Burns

When parenteral analgesia is no longer required, Empirin Compound with Codeine usually provides the relief needed.

HERE Sutures

Empirin Compound with Codeine is effective for visceral as well as soft tissue pain—provides an antitussive bonus in addition to its prompt, predictable analgesia.

Ⓒ III **prescribing convenience:** up to 5 refills in 6 months, at your discretion (unless restricted by state law); by telephone order in many states.

Empirin Compound with Codeine **No. 3,** codeine phosphate* 32.4 mg. (gr. ½); **No. 4,** codeine phosphate* 64.8 mg. (gr. 1). *Warning—may be habit-forming. Each tablet also contains: aspirin gr. 3½, phenacetin gr. 2½, caffeine gr. ½.

EMPIRIN® COMPOUND c̄ CODEINE

#3, codeine phosphate* (32.4 mg.) gr. ½
#4, codeine phosphate* (64.8 mg.) gr. 1

Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

SEPTEMBER 1973 • VOL. 178, NO. 3
ANSUA5

ANNALS of SURGERY

A Monthly Review of
Surgical Science and Practice
Since 1885

September and October numbers contain papers delivered at
THE 93rd ANNUAL SESSION
of the
AMERICAN SURGICAL ASSOCIATION
Los Angeles, California, April 25-27, 1973

J. B. LIPPINCOTT COMPANY

Don't mistake gold for diamonds

There is only one true line of DIAMOND-JAW® and DIAMOND-EDGES® instruments, made by our Snowden-Pencer Medical-Surgical Products Division. The difference is in the superhard jaws and edges.

Needle holders that grip tightly and prevent needle rotation. Scissors that cut cleanly, precisely, and stay sharp for years. These are worth imitating. But some imitators have copied only the *look* of Diamond-Jaw and Diamond-Edges instruments without the quality materials and processes that make them *perform* so well. They've gold-plated the ring handles (as we do). But we don't think a little gold will fool you if you want diamonds. Look for the Diamond-Jaw or Diamond-Edges stamp on each instrument. It's your assurance of genuineness.

Diamond-Jaw and Diamond-Edges instruments have inserts of *solid tungsten carbide*—the hardest metal made by man. Diamond-Jaw teeth are cut by diamond saws out of solid bars of the metal, to be sharper, harder, deeper than teeth formed by other methods.

Gold-plated ring handles were, and still are, a proud final touch we place on America's finest instrument line. However, others have copied this practice. Every genuine Diamond-Jaw or Diamond-Edges instrument is stamped with its brand name. Look for it before you buy, and you'll make no mistake. Available through surgical instrument dealers. Write for name of your nearest dealer.

DIAMOND-JAW Needle Holders and
Atraumatic Tissue Forceps
DIAMOND-EDGES Scissors
INSTRUMENT-MILK®
Products of SNOWDEN-PENCER
Medical-Surgical Products Division
Parke, Davis & Company
Detroit, Michigan 48232

PARKE-DAVIS

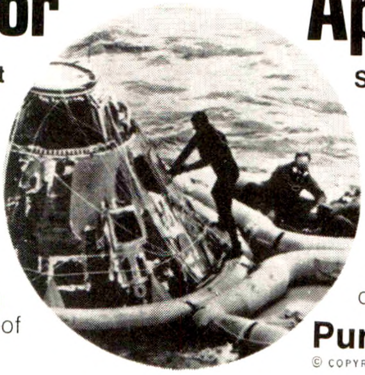
UNIVERSITY OF MEDICINE
LIBRARY
C. U.

BETADINE MICROBICIDES

Chosen by NASA for Apollo splashdowns!

When potential moon germs were a threat NASA had selected a broad-spectrum BETADINE microbicide for decontamination of the lunar capsules in Apollo 11/12/14 splashdowns.

Now NASA again selects a BETADINE microbicide for environmental protection of Skylab astronauts against infection. BETADINE Solution is circling the earth in orbit, to be used regularly for disinfection of certain equipment and for contingencies.



Sky-high microbicidal efficacy plus down-to-earth convenience distinguishes BETADINE antiseptics. They *kill* bacteria (gram-positive and gram-negative), fungi, viruses, protozoa and yeasts. Yet they are virtually nonstinging, nonirritating and do not stain skin, mucosa, or natural fabrics. And they are available in a variety of forms, designed and formulated for specific uses.

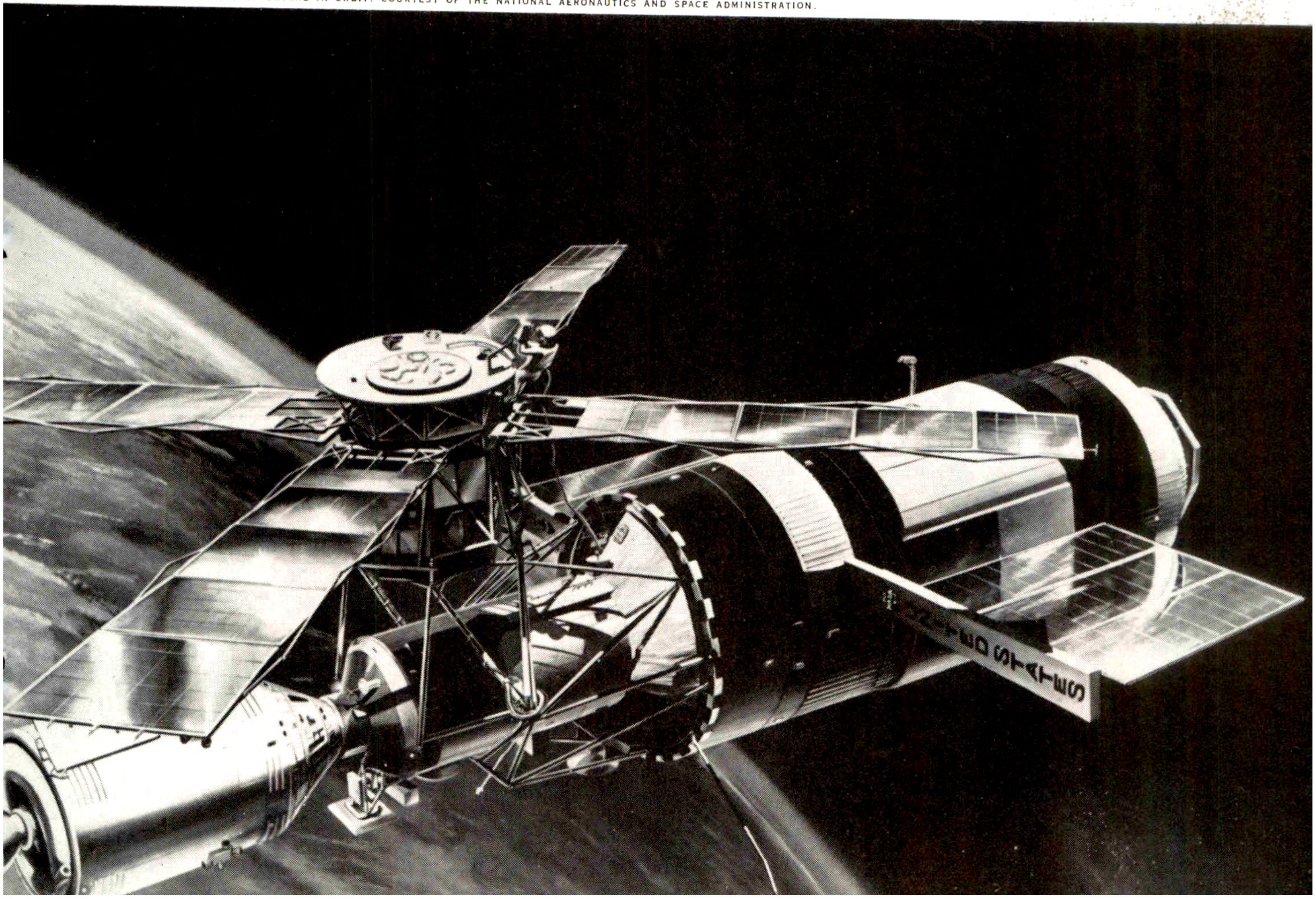
Purdue Frederick

© COPYRIGHT 1973, THE PURDUE FREDERICK COMPANY/NORWALK, CONN. 06856

A7192 135273

Chosen by NASA for Skylab mission!

ILLUSTRATION: ARTIST'S CONCEPT OF SKYLAB IN ORBIT. COURTESY OF THE NATIONAL AERONAUTICS AND SPACE ADMINISTRATION.



To help make the return

The versatility of Phenergan can make it a useful medication following surgery, both in the recovery room and back in the ward.

Phenergan helps you prevent and control nausea and vomiting associated with certain types of anesthesia and surgery. Also, Phenergan may be given as an adjunct to analgesics to help control postoperative pain.*

In addition, you can use Phenergan to help provide sedation. It helps allay apprehension and provide a light sleep from which your patients can be easily awakened.

You can even administer Phenergan IM or IV.†

Phenergan. Versatile.

INJECTION

PHENERGAN®

(PROMETHAZINE HCl)

Wyeth

*Because Phenergan adds to the sedative effects of CNS depressants, including narcotics, such agents should either be eliminated or used in reduced dosage in the presence of promethazine.

trip a smooth one.

Indications: Promethazine HCl injection is indicated when the oral form is impractical for: Amelioration and prevention of allergic reactions to blood or plasma in patients with known history of such reactions; in anaphylaxis as an adjunct to epinephrine and other standard measures after acute symptoms have been controlled; for other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated; active treatment of motion sickness; preoperative, postoperative and obstetric (during labor) sedation; prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery; as an adjunct to analgesics to control postoperative pain; for sedation and relief of apprehension and to produce light sleep from which the patient can be easily aroused; intravenously in special surgical situations (e.g. repeated bronchoscopy, ophthalmic surgery, poor-risk patients) with reduced amounts of meperidine as adjunct to anesthesia and analgesia.

Contraindications: Contraindicated in individuals with known hypersensitivity to promethazine. Intra-arterial injection is contraindicated.

Warnings: The sedative action of promethazine is additive to the sedative effects of CNS depressants; therefore, agents as alcohol, barbiturates and narcotic analgesics should be eliminated or given in reduced dosage in presence of promethazine. When given concomitantly with promethazine reduce dose of barbiturates by at least ½ and dose of analgesic depressants (e.g. morphine or meperidine) by ¼ to ½. Although proper IV use of promethazine is well-tolerated, exercise care not to allow perivascular extravasation since under such circumstances chemical irritation may occur[†] When used IV, give in a concentration no greater than 25 mg./cc. and at a rate not over 25 mg./minute.

Precautions: Caution ambulatory patients against driving autos or operating dangerous machinery until it is known that they do not become drowsy or dizzy from promethazine. Antiemetics may mask symptoms of unrecognized disease and thus interfere with diagnosis. Patients in pain who received inadequate or no analgesia have developed "athetoid-like" movements of the upper extremities following parenteral promethazine. These symptoms usually disappear on adequate control of pain.

Adverse Reactions: Patients may occasionally complain of autonomic reactions, e.g. dryness of mouth, blurring of vision and rarely dizziness. Very rare cases have been reported where patients receiving promethazine developed leukopenia. In one instance agranulocytosis has been reported. In nearly every instance reported other toxic agents known to have caused these conditions were associated with administration of promethazine. Cardiovascular by-effects from promethazine have been rare (minor increases in blood pressure, occasional mild hypotension). Photosensitivity (extremely rare) contraindicates further use of promethazine or related drugs. Attempted suicides with promethazine resulted in deep sedation, coma, rarely convulsions and cardiorespiratory symptoms compatible with depth of sedation. A paradoxical reaction (hyperexcitability and nightmares) has been reported in children receiving large single doses.

Composition: Injection—1 cc. ampuls of 25 mg./cc. and 50 mg./cc. Each cc. also contains 0.1 mg. disodium edetate, 0.04 mg. calcium chloride and not more than 0.25 mg. sodium metabisulfite and 5 mg. phenol with sodium acetate buffer.

Wyeth Laboratories **Philadelphia, Pa.**

situation:

Post-operative . . . recent surgery . . . still confined to bed . . . or restricted ambulation . . .

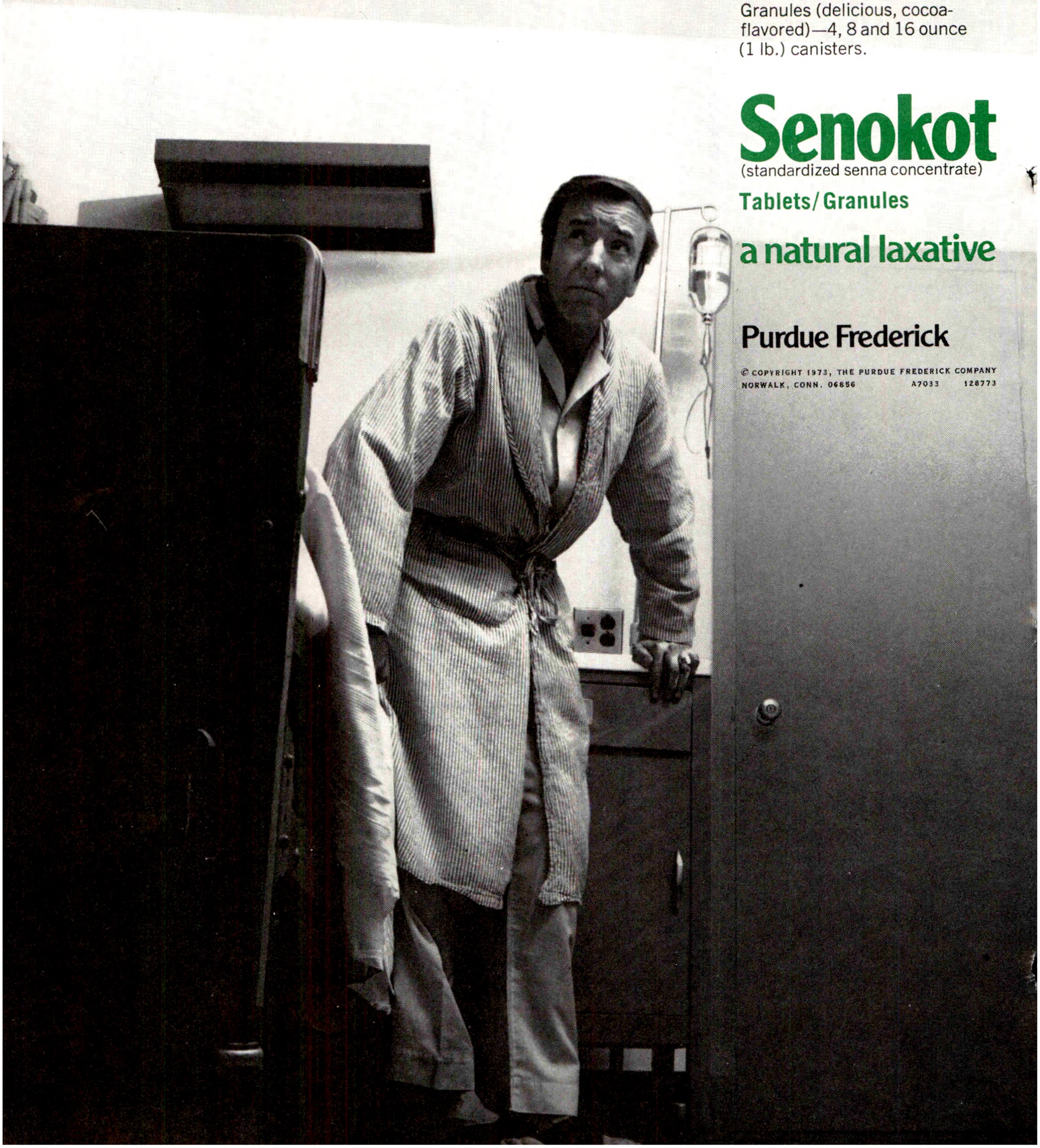
constipation:

Constipating analgesics and sedatives . . . immobilization . . . reduced food and fluid intake . . . constipation common . . . fecal impaction a threat to be avoided . . .

laxation:

Gentle and predictable with colon-specific SENOKOT Tablets/Granules. Virtually free from side effects in appropriate dosage.

Supplied: SENOKOT Tablets (small, easy-to-swallow)—Bottles of 50 and 100. SENOKOT Granules (delicious, cocoa-flavored)—4, 8 and 16 ounce (1 lb.) canisters.



Senokot
(standardized senna concentrate)
Tablets/Granules

a natural laxative

Purdue Frederick

© COPYRIGHT 1973, THE PURDUE FREDERICK COMPANY
NORWALK, CONN. 06856 A7033 128773

Annals of Surgery

A Monthly Review of Surgical Science and Practice

Also the official publication of
THE AMERICAN SURGICAL ASSOCIATION
THE SOUTHERN SURGICAL ASSOCIATION
PHILADELPHIA ACADEMY OF SURGERY
NEW YORK SURGICAL SOCIETY

EDITORIAL AND ADVISORY BOARD

JONATHAN E. RHOADS, M.D., *Chairman*
Philadelphia, Pa.

FRANK F. ALLBRITTEN, JR., M.D.
Kansas City, Kan.

WILLIAM A. ALTEMEIER, M.D.
Cincinnati, O.

W. GERALD AUSTEN, M.D.
Boston, Mass.

HENRY T. BAHNSON, M.D.
Pittsburgh, Pa.

BRIAN B. BLADES, M.D.
Washington, D. C.

WARREN H. COLE, M.D.
Asheville, N. C.

MICHAEL E. DE BAKEY, M.D.
Houston, Tex.

J. ENGLEBERT DUNPHY, M.D.
San Francisco, Calif.

FRANK L. A. GERBODE, M.D.
San Francisco, Calif.

FRANK GLENN, M.D.
New York, N. Y.

FRASER N. GURD, M.D.
Ottawa, Can.

JOHN W. KIRKLIN, M.D.
Birmingham, Ala.

WILLIAM P. LONGMIRE, JR., M.D.
Los Angeles, Calif.

LEONARD D. MILLER, M.D.
Philadelphia, Pa.

FRANCIS D. MOORE, M.D.
Boston, Mass.

JOHN H. MULHOLLAND, M.D.
New York, N. Y.

WILLIAM H. MULLER, JR., M.D.
Charlottesville, Va.

JOHN S. NAJARIAN, M.D.
Minneapolis, Minn.

WILLIAM F. RIENHOFF, JR., M.D.
Baltimore, Md.

PAUL S. RUSSELL, M.D.
Boston, Mass.

DAVID C. SABISTON, JR., M.D.
Durham, N. C.

JOHN A. SCHILLING, M.D.
Oklahoma City, Okla.

G. THOMAS SHIRES, M.D.
Dallas, Tex.

HARRIS B. SHUMACKER, JR., M.D.
Indianapolis, Ind.

FRANK C. SPENCER, M.D.
New York, N. Y.

JOHN D. STEWART, M.D.
Buffalo, N. Y.

NATHAN A. WOMACK, M.D.
Chapel Hill, N. C.

J. B. LIPPINCOTT COMPANY, *Publishers*
Philadelphia and Toronto

Second-class postage paid at Philadelphia, Pa., and at additional mailing offices

© Copyright 1973, J. B. Lippincott Company, East Washington Square, Phila., Pa. 19105, Printed in U

UNIVERSITY COLLEGE OF MEDICINE
LIBRARY

ANNALS OF SURGERY

Vol. 178 SEPTEMBER 1973 No. 3

CONTENTS

227 Presidential Address: The Quality of Surgical Scholarship, *Jonathan E. Rhoads*

232 Biologic Fate of Autogenous Vein Implants as Arterial Substitutes: Clinical, Angiographic and Histopathologic Observations in Femoro-Popliteal Operations for Atherosclerosis, *D. Emerick Szilagyi*, M.D., *Joseph P. Elliott*, M.D., *John H. Hageman*, M.D., *Roger F. Smith*, M.D., *Carlo A. Dall'Olmo*, M.D., Detroit, Michigan

247 Fifteen-Year Clinical Experience with the Vena Cava Filter, *Marion S. DeWeese*, M.D., *Richard O. Kraft*, M.D., *W. Kirt Nichols*, M.D., *Herbert H. Six*, M.D., *Norman W. Thompson*, M.D., Ann Arbor, Michigan

258 Results of Carotid Endarterectomies for Transient Ischemic Attacks—Five Years Later, *James A. DeWeese*, M.D., *Charles G. Rob*, M.D., *Richard Satran*, M.D., *David O. Marsh*, M.D., *Robert J. Joynt*, M.D., *David Summers*, M.D., *Caren Nichols*, BSN, Rochester, New York

265 Physiologic Consequences of Positive End-Expiratory Pressure (PEEP) Ventilation, *Samuel R. Powers, Jr.*, M.D., *Richard Mannal*, M.D., *Matthew Neclerio*, M.S., *Mark English*, B.S., *Clifford Marr*, B.S., *Robert Leather*, M.D., *Hidehiko Ueda*, M.D., *Gary Williams*, M.D., *Wayne Custead*, PH.D., *Robert Dutton*, M.D., Troy, New York

273 Hiatus Hernia: A 20-year Retrospective Survey, *P. R. Allison*, Oxford, England

277 Experimental Esophageal Lye Burns: II. Correcting Established Strictures with Beta-Aminopropionitrile and Bougienage, *John W. Madden*, M.D., *William M. Davis*, M.D., *Cooley Butler, II*, M.D., *Erle E. Peacock, Jr.*, M.D., Tucson, Arizona

285 Divergent Nature of Gastric Mucosal Permeability and Gastric Acid Secretion in Sick Patients with General Surgical and Neurosurgical Disease, *Michael J. Gordon*, M.D., *John J. Skillman*, M.D., *Nicholas T. Zervas*, M.D., *William Silen*, M.D., Boston, Massachusetts

295 Effect of Proximal Gastric, Complete Gastric, and Truncal Vagotomy on Canine Gastric Electric Activity, Motility, and Emptying, *Bruce G. Wilbur*, M.D., *Keith A. Kelly*, M.D., Rochester, Minnesota

304 Measurement of Endogenous Release of Cholecystokinin by Radioimmunoassay, *David D. Reeder*, M.D., *Horst D. Becker*, M.D., *Nancy J. Smith*, B.S., *Phillip L. Rayford*, PH.D., *James C. Thompson*, M.D., Galveston, Texas

311 Superiority of Antiperistaltic Jejunal Segments in Management of Severe Dumping Syndrome, *John L. Sawyers*, M.D., *J. Lynwood Herrington, Jr.*, M.D., Nashville, Tennessee

All of these mammals, except one, can synthesize vitamin C.

Man cannot.

Homo sapiens can neither synthesize vitamin C nor store most of the water soluble vitamins. They should be replenished every day.

Normally, man accomplishes this in his daily diet. But under conditions of illness, stress, in convalescence or following surgery, vitamin stores may be depleted or metabolic demands increased.

In such cases, Surbex-T may be indicated. Each tablet provides 500 mg. of vitamin C plus high potency B-complex.

Where nutritional status must be preserved, Surbex-T can help restore what the body can *not* store.

306399R

SURBEX-T® 500 mg. of Vitamin C with High Potency B-Complex

Restores what the body cannot effectively store

CONTENTS *Continued*

322 Significance and Treatment of Occult Obstructive Uropathy Complicating Crohn's Disease, *George E. Block,* M.D., M.S. (Surg), F.A.C.S., *Warren E. Enker,* M.D., *Joseph B. Kirsner,* M.D., PH.D., Chicago, Illinois

333 Carcinoma of the Extrahepatic Biliary Tract, *William P. Longmire, Jr.,* M.D., *Michael S. McArthur,* M.D., *Elias A. Bastounis,* M.D., *Jonathan Hiatt,* B.A., Los Angeles, California

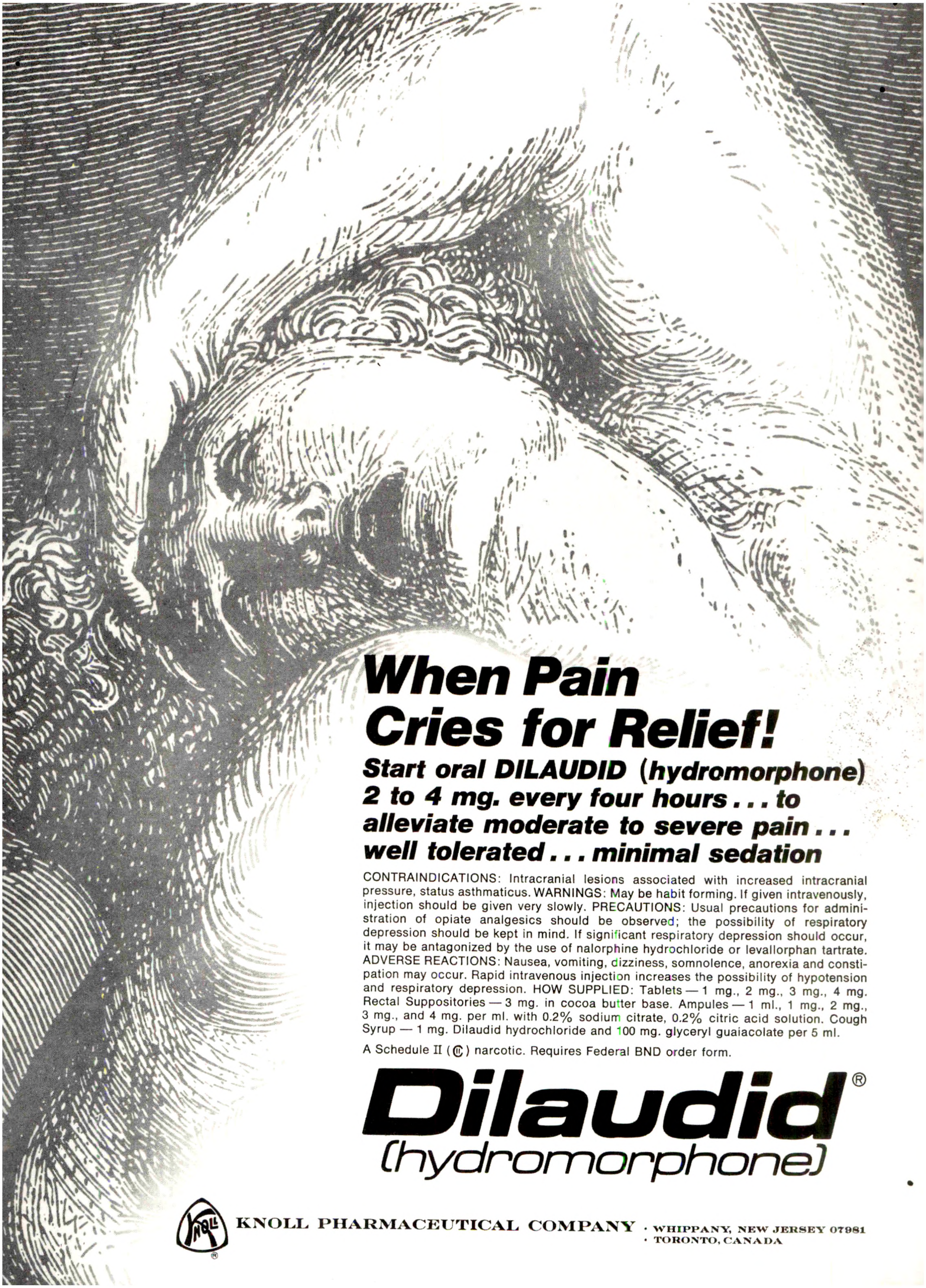
346 Reasonable Surgery for Rhabdomyosarcoma: A Study of 67 Cases, *James W. Kilman,* M.D., *H. William Clatworthy, Jr.,* M.D., *William A. Newton, Jr.,* M.D., *Jay L. Grosfeld,* M.D., Indianapolis, Indiana

352 Immunotherapy in Patients with Melanoma, *H. F. Seiger, W. W. Shingleton, R. S. Metzgar, C. E. Buckley, III, P. M. Bergoc,* Durham, North Carolina

360 Surgical Resection and Adjunctive Immunotherapy for Selected Patients with Multiple Pulmonary Metastases, *Donald L. Morton,* M.D., *William L. Joseph,* M.D., *Alfred S. Ketcham,* M.D., *Glenn W. Geelhoed,* M.D., *Paul C. Adkins,* M.D., Los Angeles, California

367 A New Approach to Colonic Polyps, *William I. Wolff,* M.D., *Hiromi Shinya,* M.D., New York City

379 Surgical Intervention for the Complications of Acute Myocardial Ischemia, *E. D. Mundth,* M.D., *M. J. Buckley,* M.D., *R. C. Leinbach,* M.D., *H. K. Gold,* M.D., *W. M. Daggett,* M.D., *W. G. Austen,* M.D., Boston, Massachusetts



When Pain Cries for Relief!

Start oral DILAUDID (hydromorphone) 2 to 4 mg. every four hours . . . to alleviate moderate to severe pain . . . well tolerated . . . minimal sedation

CONTRAINDICATIONS: Intracranial lesions associated with increased intracranial pressure, status asthmaticus. WARNINGS: May be habit forming. If given intravenously, injection should be given very slowly. PRECAUTIONS: Usual precautions for administration of opiate analgesics should be observed; the possibility of respiratory depression should be kept in mind. If significant respiratory depression should occur, it may be antagonized by the use of nalorphine hydrochloride or levallorphan tartrate. ADVERSE REACTIONS: Nausea, vomiting, dizziness, somnolence, anorexia and constipation may occur. Rapid intravenous injection increases the possibility of hypotension and respiratory depression. HOW SUPPLIED: Tablets — 1 mg., 2 mg., 3 mg., 4 mg. Rectal Suppositories — 3 mg. in cocoa butter base. Ampules — 1 ml., 1 mg., 2 mg., 3 mg., and 4 mg. per ml. with 0.2% sodium citrate, 0.2% citric acid solution. Cough Syrup — 1 mg. Dilaudid hydrochloride and 100 mg. glyceryl guaiacolate per 5 ml.

A Schedule II (Ⓒ) narcotic. Requires Federal BND order form.

Dilaudid®
(hydromorphone)

KNOLL® KNOLL PHARMACEUTICAL COMPANY · WHIPPANY, NEW JERSEY 07981
· TORONTO, CANADA

Notice to Contributors and Subscribers

The ANNALS OF SURGERY considers for publication original articles only, papers which offer significant contributions to the advancement of surgical knowledge.

CONTRIBUTIONS. Original typed manuscripts and illustrations, plus three copies and 3 sets of illustrations, exchanges and book reviews should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY:

Jonathan E. Rhoads, M.D.
1000 Ravdin Institute, 3400 Spruce St.
Philadelphia, Pa. 19104

Manuscripts, as well as list of references, should be typed double spaced on one side of the paper, leaving wide margins. While every effort will be made to guard against loss, it is advised that authors retain copies of manuscripts submitted. The complete address for reprint requests should be included in the title page. All pages should be numbered.

Digits one to ten should be spelled out, except when used for units of measurement (time, weight, volume, dosage, degrees) percentage, or when decimals are involved; for numbers above ten, numerals should be used. Dorland's Medical Dictionary and Webster's International Dictionary may be used as standard references. Scientific names for drugs should be used when possible. Copyright or trade names of drugs should be capitalized. Units of measurement, *e.g.*, dosage, should be expressed in the metric system. Temperature should be expressed in degrees centigrade. Contributions in a foreign language, when accepted, will be translated and published in English.

Black and white illustrations will be reproduced free of charge, but the publisher reserves the right to establish a reasonable limit upon the number supplied. Colored illustrations will be published at the author's expense. Black and white photographs should be in the form of glossy prints. Line and wash drawings should be black on white paper, with lettering in black india ink, large enough to be readable after necessary reduction. Large or bulky illustrations should be accompanied by smaller glossy reproductions of the same, to facilitate their circulation among the reviewing members of the editorial board. Illustrations should be numbered, the tops indicated, and the author's name and the title of the article in brief appear on the back. A separate typewritten sheet of legends for the illustrations should be supplied.

A bibliography of numbered references in alphabetical order should appear at the end of the manuscript with corresponding numbering in the text. Bibliographies should conform to the style of the Index Medicus with the exception that the last page number should be omitted, viz: author's name, title of article, name of journal, volume number, first page number, and year of publication in the order named.

PUBLISHER'S NOTICES

CHANGE OF ADDRESS: Please allow 60 days before date of issue for change of address. Notification should include the old as well as the new address, with indication of whether the change is temporary or permanent. Please give the name of the journal.

Copies will not be replaced without charge unless we receive a request within 60 days of the mailing in the U. S. or within 90 days in all other countries.

BUSINESS ADDRESS: Subscriptions, reprints, advertising, and all business communications should be addressed to:

ANNALS OF SURGERY
J. B. Lippincott Co.
East Washington Square
Philadelphia, Pa. 19105

Published Monthly. Subscription Rates $20.00 per year in the U. S., its possessions and Canada. All other countries $23.00. All prices include postage. Single issues $3.00. Rate for Residents, U. S. only, $14.00.

The publishers accept no responsibility for opinions expressed by contributors.

Our support hosiery looks funny for some very serious reasons.

Compare Parke-Davis Elastic Support Hosiery with another brand—one you may now be recommending. See for yourself why ours best provides these important advantages.

1. *True, controlled graduated compression* means greater support at the foot and ankle, and gradually less support higher up the leg. Ours obviously provides this feature.

2. *Two-way stretch* is woven into the hosiery from bottom to top. So there's no need for a tourniquet-like band at the top to help keep the hosiery up. Ours obviously provides this feature.

3. *Medically-correct design* matches the needs of the patient with vascular disease of the lower extremities. Ours obviously provides this feature.

Result: our support hosiery does what support hosiery should do. It helps prevent edema. Minimizes venous pooling of blood. Helps reduce the leg pain associated with varicosities.

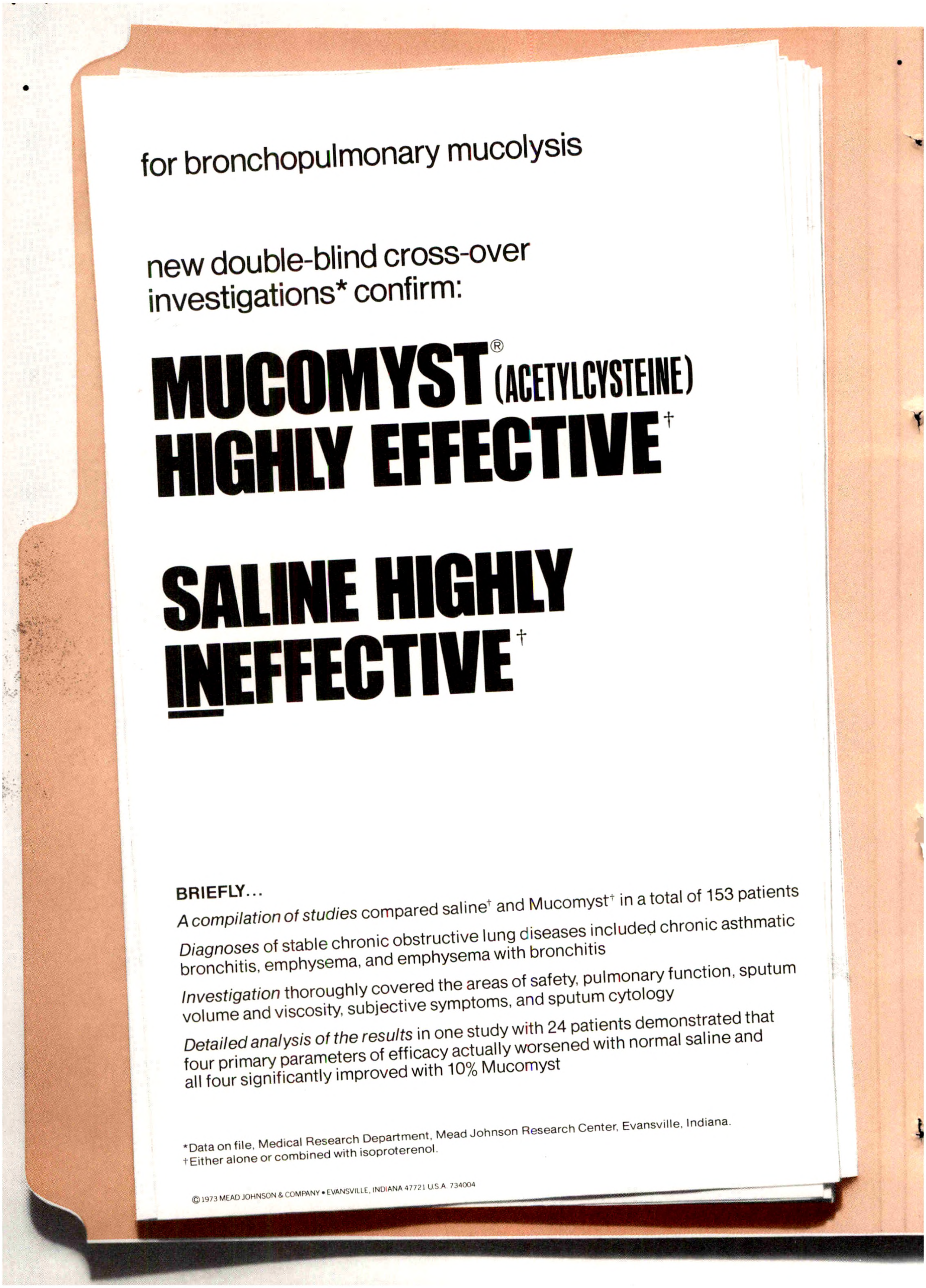
Incidentally, Parke-Davis Elastic Support Hosiery is made for women, too. Panty hose included. A complete range of sizes and sheerness. Better looking than men's hosiery—but still medically correct.

Seriously, isn't that beautiful?

PARKE-DAVIS
ELASTIC SUPPORT HOSIERY

They look funny-
until you
put them on.

Parke, Davis & Company • Detroit, Michigan 48232
PD-JA-0996-1-C (2-73)



for bronchopulmonary mucolysis

new double-blind cross-over
investigations* confirm:

MUCOMYST® (ACETYLCYSTEINE)
HIGHLY EFFECTIVE†

SALINE HIGHLY
INEFFECTIVE†

BRIEFLY...

A compilation of studies compared saline† and Mucomyst† in a total of 153 patients

Diagnoses of stable chronic obstructive lung diseases included chronic asthmatic bronchitis, emphysema, and emphysema with bronchitis

Investigation thoroughly covered the areas of safety, pulmonary function, sputum volume and viscosity, subjective symptoms, and sputum cytology

Detailed analysis of the results in one study with 24 patients demonstrated that four primary parameters of efficacy actually worsened with normal saline and all four significantly improved with 10% Mucomyst

---

*Data on file, Medical Research Department, Mead Johnson Research Center, Evansville, Indiana.
†Either alone or combined with isoproterenol.

© 1973 MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA 47721 U.S.A. 734004

MUCOMYST VS. SALINE

COUGH FREQUENCY
at first decreased, then increased with saline...*consistently reduced* with Mucomyst

WHEEZE SEVERITY
increased with saline...*significantly reduced* with Mucomyst

SPUTUM VISCOSITY
increased with saline...*significantly thinner* with Mucomyst

EXPIRATORY PHASE PROLONGATION
a good index of airways obstruction—increased or remained unchanged with saline...*significantly reduced* with Mucomyst

One double-blind cross-over study which included analysis of 52 variables compared the effects of one week of normal saline therapy with the effects of one week of 10% Mucomyst in each of 24 patients.

	Variables	
	Improved	Worsened
Mucomyst	13	2
Saline	4	5

While large changes cannot be expected after one week's therapy in patients with stable chronic obstructive lung disease, of the variables that changed significantly with saline therapy, more worsened than improved. However, of the variables that changed significantly with Mucomyst, the great majority were *improvements* in the patients' status.

CONCLUSIONS

- Mucomyst decreases sputum viscosity—saline *at best* effects no change
- Mucomyst *reduces* frequency of cough and severity of wheezing—saline *increases* them
- Mucomyst *reduces* the length of the expiratory phase—saline causes no change or increases it

Therapeutic compatibility of Mucomyst with isoproterenol and other bronchodilators has been demonstrated in double-blind controlled studies totaling 134 patients. No untoward effects requiring cessation of Mucomyst therapy were reported in these patients.

MUCOMYST® (ACETYLCYSTEINE)

Indications: Mucomyst has been demonstrated to be clinically effective as adjuvant therapy in a wide range of conditions in which thick, viscous mucus is a problem, including: postoperative atelectasis and pneumonia; chronic bronchopulmonary disease (emphysema, chronic bronchitis, asthmatic bronchitis, and bronchiectasis); acute bronchopulmonary disease (pneumonia, bronchitis, and tracheobronchitis); tracheostomy care; facilitation of bronchial studies; maintenance of an open airway during anesthesia; and to help control pulmonary complications of cystic fibrosis. **Contraindications:** Mucomyst is contraindicated in those patients who are sensitive to it. **Warnings:** *After proper administration of acetylcysteine, an increased volume of liquefied bronchial secretions may occur. When cough is inadequate, the open airway must be maintained by mechanical suction if necessary. When there is a large mechanical block due to foreign body or local accumulation, the airway should be cleared by endotracheal aspiration, with or without bronchoscopy. Asthmatics under treatment with Mucomyst should be watched carefully. If bronchospasm progresses, this medication should be immediately discontinued.* **Adverse Effects:** Adverse effects have included stomatitis, nausea and rhinorrhea. Sensitivity and sensitization to Mucomyst have been reported very rarely. A few susceptible patients, particularly asthmatics (see *Warnings*), may experience varying degrees of bronchospasm associated with the administration of nebulized acetylcysteine. Most patients with bronchospasm are quickly relieved by the use of a bronchodilator given by nebulization. **Administration:** Mucomyst may be administered by nebulization into a tent, Croupette, face mask, or mouthpiece, or by direct instillation. *Mucomyst should not be placed directly into the chamber of a heated (hot pot) nebulizer.* Complete details on dosage, administration, and compatibility are included in the package insert. Additional information may be obtained from Mead Johnson Laboratories. **Supplied:** *Mucomyst®-10 (acetylcysteine)* a sterile 10% solution in vials of 10 ml. and 30 ml.: *Mucomyst® (acetylcysteine)* a sterile 20% solution in vials of 10 ml. and 30 ml.

Mead Johnson
LABORATORIES

The sensitive touch of talent comes through with our soft-dipped latex. Hands performing in TRIFLEX® Surgeon's gloves move more freely throughout a lengthy surgical procedure. That's because the patented TRAVENOL mold contours gloves with natural shaping, right from the wrist. Result: more freedom from strain against the thumb joint, stress across the palm. Fingertips are tapered for finer fit.

Matte finish provides a good grip on instruments—less slippery when wet, and it won't get tacky.

PowderIN processing cures powder right onto the latex, on the inside surface. Try the dark suit powder demonstration test with your TRAVENOL representative,

Each pair is packaged in a handy waterproof plastic tray with Tyvek* lid . . . in compact dispenser cartons, for convenience and easy storage. Start a glove affair with TRIFLEX. Call your TRAVENOL representative today.

Recognition for the independent thumb

The contour molded thumb means more freedom from strain and stress caused by restrictive 2-plane molded gloves.

*® DuPont

CAUTION: After donning, remove powder by wiping gloves thoroughly with a sterile wet sponge, sterile wet towel, or other effective method.

TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015

Glove story
...softer
with feeling

TRAVENOL
SURGEONS'
GLOVES-
SENSITIVITY WITHOUT
CRAMPING
YOUR STYLE

Brief Summary.
Consult the package literature for prescribing information.

Actions: Keflin® (sodium cephalothin, Lilly) is a broad-spectrum antibiotic. Following a single 1-Gm. intravenous dose, blood levels have been about 30 mcg. per ml. at fifteen minutes. Dosages of 2 Gm. given intravenously over a thirty-minute period have produced serum concentrations of 80 to 100 mcg. per ml. one-half hour after the infusion.

The antibiotic passes readily into body fluids, e.g., pleural, joint, bile, and ascitic fluids.

Indications: Keflin is indicated for the treatment of serious infections caused by susceptible strains of the designated micro-organisms in the diseases listed below.

Respiratory tract infections caused by *Diplococcus pneumoniae*, staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Klebsiella*, and *Hemophilus influenzae*

Skin and soft-tissue infections, including peritonitis, caused by staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella*

Genito-urinary tract infections caused by *Esch. coli*, *Pr. mirabilis*, and *Klebsiella*

Septicemia, including endocarditis, caused by *D. pneumoniae*, staphylococci (penicillinase and nonpenicillinase-producing), group A beta-hemolytic streptococci, *Streptococcus viridans*, *Esch. coli*, *Pr. mirabilis*, and *Klebsiella*

Gastro-intestinal infections caused by *Salmonella* and *Shigella* species

Meningitis caused by *D. pneumoniae*, group A beta-hemolytic streptococci, and staphylococci (penicillinase and nonpenicillinase-producing)

Bone and joint infections caused by staphylococci (penicillinase and nonpenicillinase-producing)

Contraindication: Previous hypersensitivity to cephalosporins.

Warnings: BEFORE CEPHALOTHIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY IN PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Severe anaphylactoid reactions have been reported with both drugs.

Patients with allergy and hypersensitivity should receive antibiotics cautiously and only when necessary.

Usage in Pregnancy—Safety for use during pregnancy has not been established.

Precautions: Patients should be followed carefully to detect any side-effects or drug idiosyncrasy. If an allergic reaction occurs, discontinue the drug and treat the patient with usual agents.

Although alteration in kidney function is rare, evaluation of renal status is recommended. Patients with impaired renal function should be placed on a reduced dosage schedule to prevent excessive serum concentrations. Consult prescribing information.

If thrombophlebitis or superinfection occurs, take appropriate measures. A false-positive reaction for glucose in the urine has been observed with some tests but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: Maculopapular rash, urticaria, pain, induration, tenderness, elevation of temperature, reactions resembling serum sickness, anaphylaxis, eosinophilia, drug fever, neutropenia, thrombocytopenia, hemolytic anemia, thrombophlebitis, transient rise in SGOT and alkaline phosphatase, rise in BUN, decreased creatinine clearance, and a positive direct Coombs test have been reported. [071873]

on the surgical service...

Keflin® I.V.
sodium cephalothin
2 Gm.* in 100-ml. ampoule
*equivalent to cephalothin

10 years of
clinical
experience

Additional information
available to the
profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

Lilly

301104

on the surgical service...

Keflin® I.V.
sodium cephalothin
2 Gm.* in 100-ml. ampoule

10 years of clinical experience

Keflin was made available for clinical investigation early in 1962 and was marketed on September 4, 1964.

Since the introduction of Keflin, the susceptibilities of commonly encountered organisms, as measured by in-vitro methods, have not changed significantly. See brief summary for indications.

Lilly

*equivalent to cephalothin

Please turn page for summary of prescribing information.

ANNALS OF SURGERY

Vol. 178 September 1973 No. 3

Presidential Address:

The Quality of Surgical Scholarship

JONATHAN E. RHOADS

MY GRATITUDE to the members of the Association is very great. It stems not only from the immense honor of serving as your President, but also for the privilege of becoming a member comparatively early. This enabled me to hear and meet surgical leaders from areas of the country away from my own home such as: Evarts Graham, Roscoe Graham, W. Edward Gallie, Fred Coller, Howard Naffziger, Fraser Gurd, Sr., Allen Whipple, Dallas Phemister, Frank Lahey, Henry Cave, Dan Elkin, Richard Cattell, Howard Cray, Samuel Harvey, Harvey Cushing, and many others.

On two occasions the Association asked me to serve as its representative to the National Research Council which brought many welcome contacts with people in other disciplines. An even more significant assignment came in 1969 when Owen Wangensteen asked me to chair a committee on the purpose and function of the American Surgical Association. I was joined on the committee by Drs. Walter F. Ballinger, II, Ben Eiseman, William D. Holden, Lloyd D. MacLean, Marshall J. Orloff, David C. Sabiston, Jr., and Bernard Zimmermann. The report of this committee reconfirmed the great value of the traditional programs of the Association. In addition, it proposed the formation of a Committee on Issues to direct attention to matters of national policy in which members of the Association had special concern and special expertise by virtue of their positions in American surgery.

Recognizing a community of interest with the American College of Surgeons which proposed a study to determine who performs the surgery for our citizens, the Study on Surgical Services for the United States, or SOSSUS as it became known, was formed as a joint endeavor of the two organizations under the able chairmanship of Dr. George Zuidema.

As you know, Dr. Francis Moore has pressed forward the surgical manpower study which he originally outlined as a vice president of the College.

It is now nearly a decade since the Congress passed the legislation providing Medicare and encouraging the states to provide Medicaid. Since 1963, when the push for this legislation gained strength, much of the non-technical thinking presented before surgical audiences has dealt with the delivery of surgical care. The problems of the mass production of surgical care, with the requisite quality control, are enormously important and we can take pride as an Association in having sponsored the SOSSUS Study.

A report on this study will be presented at a closed session of the Association at the breakfast hour tomorrow and I would urge every member who is here to attend.

The American Surgical Association has still another responsibility in society—that of not only maintaining, but wherever possible, of enhancing the quality of scholarship in the field of surgery. It might seem undemocratic to say that this was even more important, but it can be said that the American Surgical Association is peculiarly fitted to uphold and indeed to enhance the quality of surgical scholarship.

My reason for selecting this topic for emphasis is a fear that the quality of scholarship in surgery has been slipping and that in a broader sense the M.D. degree

---

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25-27, 1973.

has been demeaned in our time. Within the medical profession, is the surgeon thought of in the phrase attributed to John B. Deaver as a medical man and something more? Or, have too many who call themselves surgeons become something less?

The decline in prestige of the physician and of the surgeon is not all obvious. The caricatures in newspapers and magazines are not a new phenomenon. Some of the best of them were drawn in the 18th century and some of this sort of thing is only a kindly attempt to keep the members of a learned profession from taking themselves too seriously.

My concern is more with the question of how many of our profession are learned—or even care to be. This year I am completing a brief term as Chairman of the Editorial Board of the *Annals of Surgery*. In this capacity I have read a good many hundred manuscripts. These are supposed to be original articles. Most of them are, but some represent relatively little addition to a data base provided by earlier authors.

Furthermore, some have to be turned down because they have actually been published elsewhere. Some reflect the work of others without acknowledging it. A considerable portion of the material submitted is dotted with errors in spelling, in grammar, and in sentence structure. When one particularly poorly written paper was returned, I suggested to the author that he had not read the final draft. He wrote back, apologizing for the errors and stating that it had come off an automatic typewriter and that, in point of fact, he had not read the draft that was submitted. Since an automatic typewriter has no will of its own, I was reminded of the slogan of the computer programmers—"Garbage in-garbage out," and rather concluded that he had not read the draft that went into the typewriter either.

Other papers submit experimental data without controls or with purported controls that do not permit conclusions. Still others may present good data, but without sufficient statistical analysis to permit the reader to know what the probability of error in the conclusions may be.

These errors are cited partly to illustrate what is meant by unscholarly work. Some of the errors are purely intellectual; some violate the ethics of scholarship.

When we speak of a scholarly person, however, we mean still more. We think of someone who reads purposefully and also widely. We think of one who can read in more than one language, of one who organizes his knowledge, so as to have rapid recall of it—this is what the computer experts call random access. We think of persons who keep their knowledge alive by constantly adding to it, both by reading, by word of mouth, and by experiment.

Such individuals are reminiscent of the man blessed in the first psalm who 'delighteth in the law of the Lord and in His law doth he meditate day and night.'

Thus, there are elements of enthusiasm and of energy in being a scholar, elements that were so prominent in a man such as Rudolf Matas as to almost separate him from his fellows. The tradition is that his Presidential Address lasted several hours and I personally heard him give a 45-minute discussion.

Scholars are not all very imaginative. Fortunately, many of them are. Others serve as critics of the work of less careful investigators, showing their errors and reducing their claims to those which will in fact stand up.

Near the end of his life, Evarts Graham submitted a paper entitled "Considerations of Bronchogenic Carcinoma," to the *Annals of Surgery*. He was the sole author. Not only was it highly significant in its thought content, but in reading it carefully I could not identify a single error in spelling, in grammar, or in typing. Perhaps we should honor his secretary for this achievement, but we must honor Dr. Graham for caring enough about accuracy to provide for such a result.

In reading manuscripts for this journal for over 25 years, I believe this was the only one that was truly letter perfect—and it came from one of the busiest surgeons in the United States.

These random experiences as an editor serve to alert one to a danger, but they are, after all, a very small sample.

More significant are certain trends evident in the actions of governments—from University governments to the Federal Government.

To begin with, most politicians and government staff members describe what they want in quantity, as medical care of the highest quality, of course! This is a contradiction in terms. By using the superlative, one eliminates any practical possibility of reaching this objective.

One might say I was being pedantic and that everyone knows what we mean. This can be challenged—it is very doubtful that everyone knows what we mean, or that everyone who glibly uses the phrase "highest quality, of course" means the same thing at all. I have even heard a Medical School Dean say that Dr. X, a candidate to chair a clinical department, who admittedly had an impressive bibliography, must be an accomplished clinician because he has passed the Board examinations in his specialty.

We need to drop the superlative and accept the term high quality care and then focus on defining this.

One of the thrusts of the Millis Commission Report was that the specialties were requiring too long a period of education and/or training. In the report, and in the wake of the report, have been numerous proposals to foreshorten such time requirements. Let me add these up.

One is a proposal to compress the four years of college and the four years of medical school to 6 years total. The internship, which often ran two years, was compressed during World War II to one year and the second year was never restored.

The American Board of Surgery, I believe, required five years beyond internship when it started in 1937. Soon it reduced this to four years beyond an internship and recently accepted the first year after the M.D. to be counted concurrently with the first year of residency. Thus, many graduates of medical school in the 30's had 4 + 4 + 2 + 5 = 15 years after high school before becoming Board eligible in general surgery. Now it can be done on a 6 + 4 = 10 year after high school basis.

Curricular changes in medical school are very widespread. The emphasis has been on giving the student what seems relevant to him, and in general to foreshorten required courses and replace them with either elective courses or the duties formerly assigned to interns.

The familiar designation of a subject area as a discipline is, of course, not a chance usage. It stems from the fact that thorough knowledge of a subject requires the necessary discipline to study the dull parts as well as the interesting parts, to learn many of the factual details from which the principles have been deduced, rather than to acquire merely a facile acquaintance with the principles, devoid of the basis of observation on which they stand.

So seldom do students, once admitted to medical school, flunk out, that there is the opportunity for a student to become something of a dilettante in his medical studies. It is a reassuring observation that so few of them do.

The specialty training programs, on the other hand, and especially those in surgery, are extremely demanding. As pointed out by Dr. J. D. Martin in his Presidential Address to the Southern Surgical Association in 1968, those who are training directors have a special responsibility to see to it that those going into surgery are thoroughly and not superficially educated.

Meanwhile, what is going on in other countries? I will confine my comments to the English-speaking colleges of which there are six outside of North America, plus the Canadian Royal College of Medicine and Surgery. All of these seven are examining bodies. It was my privilege to sit in on three basic science examinations and three clinical examinations in Capetown in 1972. Anatomy was conspicuously rigorous—too rigorous in my judgment, but on the other hand, we certify some surgeons with a frightening ignorance in this field. Physiology was quite similar to ours, and the clinical exams were perhaps sterner, but covered the same kind of material.

The discussion which took place at the meeting of the representatives of the English-speaking Colleges, however, was not about shortening the period of training, but about lengthening it. The Australians were especially insistent that the Colleges in Great Britain depended too much on the examination and too little on clinical experience. The four surgical colleges in the British Isles are coming together on a common advanced specialty exam, for which any one of their four fellowships would be a necessary prerequisite.

Turning again to governmental attitudes, in the original Medicare legislation, persons over 65 were eligible for hospital care and on payment of a small fee, to a large measure of professional care. It was further provided that the Federal government would make matching grants to states to provide similar service to the "medically indigent" under the age of 65. The law provided that such state programs would lose their Federal matching if they did not improve their benefits by 1972 to be equal to those under medicare for persons over 65.

1972 has come and gone; this condition has in general not been met and under subsequent government decisions appears no longer to be required. Perhaps the original law was not realistic, but the change does represent a retreat from the earlier objective of giving every patient the status of a private patient of a physician, as opposed to being the ward of a hospital.

In the present scene we see increasing opposition to the participation of physicians in governing boards of Blue Cross plans, efforts to decrease their representation on Blue Shield plans, sluggish progress in adding them to the governing boards of hospitals. Instead we see mounting pressures to load the physicians with frequent, long handwritings on hospital records, limitless conferences with patients under the American Hospital Association's Patients Bill of Rights—in short, mounting pressures to make the physician an employee at a depreciating salary and to occupy his time with trivia completely enough to ablate his scholarly instincts.

In short, there are voices in government and indeed in medicine itself, calling for economy, if not at the sacrifice of quality, certainly at a risk to quality.

To those who could demean surgery or medicine for immediate economy, the American Surgical Association must speak with unmistakable clarity. The worth of good health care greatly exceeds its cost.

To this end, I believe the committee on issues should be reconstituted upon completion of the SOSSUS Study.

Many of us serving as directors of surgical training programs have been drawn into the vortex of mass production. Part of the problem has probably arisen from our effort to step up the production of surgeons and we may have overdone it. The American Board of Surgery increased the number of men certified from 438 to 1940 to 826 in 1972. Looking at certain of the academic medical centers, Halsted trained 17 senior residents between 1892 and 1922, slightly over one in two years. In addition, there were 55 others who had a year or more on his service. At the Hospital of the University of Pennsylvania approximately 79 men completed their general surgical training from 1925 to 1959, slightly over two per year. From 1959–1972, including those in the process in 1959 but not including those partially trained as of June 30, 1972, 76 completed their training in general surgery or almost six per year. I do not believe this acceleration is unique.

As shown so clearly in the analyses presented by Dr. Francis Moore, Dr. Osler Peterson, and their colleagues at our 1972 meeting, the present rate of production of surgeons, if continued, would produce a higher surgeon to population ratio than the present M.D./population ratio by the year 2000. This conclusion was based on projections of a higher population growth rate than now exist.

It seems fair to conclude, therefore, that our total number of residency positions should be decreased in the near future and that it is a time to train better surgeons rather than too many more of them. We will have a clearer fix on this as the SOSSUS manpower studies are completed.

After many years and long discussions by a number of people, there is now established a central coordinating committee and two Liaison Committees—one on undergraduate education, one in the graduate education field, that is, house officer education. There is one still to be formed on continuing education. Dr. C. Rollins Hanlon, Director of the College, is on the Senior Committee and Dr. William Holden is on the Liaison Committee on Graduate Medical Education.

Thus, for the first time in the U.S.A., there has been established a central agency which might make effective recommendations concerning the number of residency opportunities that will be accredited in each field. Within such an allotment for general surgery, for instance, the tripartite review committee might be asked to scale down either the number of hospitals approved for residency or the number of residents in each program, or both.

The American Surgical Association has been a tremendous force for quality in surgical scholarship. It has provided the most critical and the most attentive audience it has ever been my privilege to address. Few members send abstracts for consideration of the program committee unless they have mature papers based on new data to present. Practically without exception, those finally accepted are splendid examples of surgical scholarship. It is a great privilege for any of us to present a paper here and particularly so for a young surgeon who is not a member.

The privilege of having one's paper considered by so many of the leaders of American surgery, the formal discussion at the sessions, and still more the informal discussion in the halls, and the chance to meet many of the members, made an indelible impression on me as a guest at the St. Louis meeting in 1940 and has, I believe, had a stimulating effect on every young man in a similar position since.

This, our association does superbly well and must continue as a central function.

What more can we do?

In considering measures, which we might take as an Association to further strengthen our central emphasis on enhancing the quality of surgical science and art, the following possibilities are suggested.

Our programs are drawn almost entirely from North America. This is our forum and it is right that most of the 33 or 34 places on the program continue to be available to our own constituency. However, those of us who have had the opportunity of attending meetings with the Surgical Research Society of Great Britain and the European Society for Experimental Surgery are acutely aware of the excellence of some of the work going forward in Europe. Travel in other parts of the globe indicates parallel activity.

We could, I believe, benefit from greater input from abroad. Like the Committee on Issues, the addition of a class of corresponding members occurred in 1970, stemming in part from the review of the Association's purposes and procedures which Owen Wangensteen instigated the preceding year. The objective was to join with us kindred spirits from overseas who are in the full swing of their most productive years—persons some of whom might become honorary members later, but probably by that time would have passed their most productive periods. Whether or not this dual nomenclature will prove acceptable in the long run, the objective of drawing in a few of the active contributors to surgical science abroad is excellent. Unfortunately, travel costs are a real impediment to the success of this program. Many of those recommended by the Honors Committee and the Council cannot afford to come, and the Association has never budgeted to bring speakers from abroad.

Another possible means of increasing our emphasis on surgical scholarship would be to offer an annual prize for the best paper presented each year by a non-member under 45. Such a prize might consist in provision for a travelling fellowship, which could provide the recipient with an appropriate reason to take three months, six months, or longer off from his routine duties for study abroad, and fund his journey or a substantial part of it.

Finally, could we initiate a plan which would more clearly identify the good surgeon who is also an accomplished and contributing scholar from the good surgeon who uses the knowledge made available by others, but does not undertake the task of adding to it.

Perhaps logic would dictate that we become bachelors of medicine at the end of medical school, masters of surgery at the end of a minimal surgical training, and only gain the Doctor of Medicine degree for carrying out advanced study and research.

I am afraid we cannot turn the clock back to regain this logical stance. In the United States, the M.D. has become the standard credential for the practice of medicine at the primary care level, as well as in the specialties. Yet the difference is real, and the student who has the ability, the ambition, the energy, and the determination to become a contributor to productive scholarship in our field deserves recognition in a form which is easily understood by the public, such as an additional academic degree. I propose that a small Ad Hoc Committee be established to study this problem and report its findings and recommendations to the Association.

Several of the foregoing proposals cost money—particularly those involving foreign travel. I live in the belief that the prompt transfer of new knowledge in the field of surgery is important enough to justify such an expenditure. A corollary of this view is that we should resist efforts of federal, state, or university governments to set our incomes at a level at which we cannot effectively serve those purposes to which we are dedicated.

The ASA is a small organization and, in my judgment, it best fulfills its special purposes by remaining so. We have shown our willingness to increase our dues for the work of the Committee on Issues (currently the SOSSUS Study), and I hope the members may be willing to approve a continuation of this moderate contribution.

However, I do not believe we should look to dues as the major source of funds with which to pay the overseas travel costs of speakers we bring to our meetings, nor the costs of travelling fellowships or other awards we might make for the encouragement and advancement of young surgical scholars. It would seem likely, however, that these objectives could be accomplished through voluntary contributions and bequests of endowment.

To accommodate such a possibility, a small committee composed of Drs. William Altemeier, Lyman Brewer, Julian Johnson and Tom Shires has been appointed to study the tax status of the American Surgical Association to see if a mechanism such as an educational foundation could be set up through which contributors could support its educational programs with recognition of their gifts and bequests as qualifying for deduction from taxable income or estate.

Meanwhile arrangements have been made with a foundation for the support of a lecturer from overseas in each of the next two years on an interim basis, if Council after advice from the Program Committee should decide to avail themselves of it. If this plan is implemented, it would provide some experience on the basis of which longer-range plans could be based.

I would commend these suggestions for your consideration and before concluding would like to say a few words in a more personal vein.

Two years ago I heard the retiring Professor of English give the Commencement Address at Haverford College. The affection and respect of the students for him had led them to urge his selection as their speaker. Professor Frank Quinn woke me up when he said that each man's self-image is constructed of the feedback of numerous reactions from those other people who know him. I would add it is especially from those persons whom he respects the most. Together with certain members of my family and my church, you, the members of the American Surgical Association have largely constituted that circle of acquaintances for me. That you have been overgenerous, I know full well, so that I am grateful to the other groups for their more realistic appraisals and most of all to my wife for her honesty as well as her love.

May I seize this opportunity to thank you for the signal honor of serving as your president and to wish you all success, both individually and in your joint endeavors in surgery and for surgery through this Association.

In conclusion, the very simple thrust of this address is to reaffirm the belief that our central mission in world surgery is to hold high the standards of surgical scholarship and thus to advance further the rich heritage of human help by which our profession ministers to others. Our efforts to improve the distribution of medical care are of great importance and fully worthy of our earnest support, but they, nor any other goals, must not deflect us from a central emphasis on enhancing the quality of surgical care through sound scholarship.

Our first President, Samuel D. Gross, after serving as Professor of Surgery in Cincinnati, New York, and Louisville and after having turned down invitations from the Universities of Louisiana, Virginia, and Pennsylvania, finally returned to his Alma Mater, Jefferson, in 1856 at the age of 51. I will end by reading a passage from his Inaugural Address. While we might not choose these words in 1973, their message is still full of meaning.

He said: "Whatever of life and of health and of strength remain to me, I hereby, in the presence of Almighty God and of this large assemblage, dedicate to the cause of my Alma Mater, to the interest of medical science and to the good of my fellow creatures."

Biologic Fate of Autogenous Vein Implants as Arterial Substitutes:

Clinical, Angiographic and Histopathologic Observations in Femoro-Popliteal Operations for Atherosclerosis

D. EMERICK SZILAGYI, M.D., JOSEPH P. ELLIOTT, M.D., JOHN H. HAGEMAN, M.D.,
ROGER F. SMITH, M.D., CARLO A. DALL'OLMO, M.D.

From the Department of Surgery, Henry Ford Hospital, Detroit, Michigan 48202

ALTHOUGH autogenous vein grafts, the most nearly ideal arterial substitutes, are widely used and their histologic behavior is undoubtedly an important factor in determining long-range patency, little is known about their biologic fate after implantation in humans. Reports of experimental findings in autogeneic vein grafts are fairly numerous[2,4,15,18,19,21,22,28] (though often conflicting in their conclusions), but only a few isolated cases of clinical post-transplantation observations have been described[1,3,5,6,8,9,10,12,19,20] and no comprehensive study of the subject has been reported. To obtain a better understanding of the natural history of these implants, we have reviewed our experience with lower-limb atherosclerotic occlusive disease in which autogenous saphenous vein bypasses have been used during the period of 1962–1972. We report here our findings in correlating the clinical course of these cases with postoperative angiographic and histopathologic observations.

Clinical Material. Method of Study.

Case Selection. Our study is based upon 377 autogenous venous bypasses performed in the lower extremity, of which 316 were femoro-popliteal procedures and 61 were infrapopliteal (Tables 1–4, Fig. 1). In a femoro-popliteal procedures, the vein bypass graft extends from the common or proximal superficial femoral artery to the popliteal artery below the level of the knee joint. In the infrapopliteal operation, the distal anastomosis is formed between the graft and one of the branches of the popliteal artery from the point of its bifurcation to the level of the ankle. All operations were performed to correct the manifestations of atherosclerosis, almost entirely of the occlusive type.

Method of Follow-up. The patients were examined by angiographic technics before discharge from the hospital unless the operation was an obvious clinical failure, in which case the angiographic study was omitted. In a few instances, because of complications in postoperative recovery, angiographic examination was delayed for as much as 6 weeks. After discharge, angiographic study was done at 1 year postoperatively and at intervals of 1–3 years thereafter. The technic of translumbar aortography used has been described in a previous report.[24] When the proximal anastomosis was below the level of the common femoral artery, percutaneous femoral arteriography was employed frequently. Of the total number, 289 patients had patent grafts, at hospital discharge, and among these 260 had undergone at least one postoperative angiogram; 214 had undergone femoro-popliteal procedures and 46 were in the infrapopliteal subgroup. Of the combined group involving all regions of the lower extremity, 64.5% of the patients had two or more angiograms and 26.3% had undergone three or more angiographic studies (Table 5). Clinical check-up examinations were carried our at 4 weeks and 6 months postoperatively and once every year thereafter.

As of December 31, 1972, which was the closing date

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25-27, 1973.

This work has been supported in part by a grant from the Michigan Heart Association.

TABLE 1. *F-iP Venous Autografts for Occlusive Disease Immediate Results by Severity of Disease*

Grade	Total No.	Open No.	Open %	Closed No.	Closed %	Amputation No.	Amputation %	Op. Mort. No.	Op. Mort. %
I	2	2	100.0	0	0	0	0	0	0
II	13	10	76.9	1	7.7	2	15.4	0	0
III	46	36	78.3	2	4.3	7	15.2	1	2.2
Total	61	48	78.7	3	4.9	9	14.8	1	1.6

of the survey, the clinical follow-up was complete in all the patients with or without angiograms, and the angiographic follow-up was complete in all the patients examined angiographically, within 6 months of the closing date of the study. The clinical follow-up periods were considerably longer in the femoro-popliteal group, 72.2% of this group having been followed for 3 years or more and 46.5% for 5 years or more (Table 6). In femoro-infrapopliteal cases only 25% were followed clinically for 3 years or more (Table 7). The extent of angiographic follow-up disclosed similar comparative trends in the two anatomic groups.

Method of Study. For the purpose of this study, all angiographic reports prepared by the authors at the time of the original angiographic examination were reviewed. All the angiograms in the description of which some deviation from the normal had been noted were individually studied and details of the deviation were recorded. These details, together with the voluminous clinical data were transferred to punch cards and then to magnetic tape for computer manipulation.

As formerly stated, the primary aim of the study was to detect structural changes in the vein grafts that could be correlated with the clinical course. Since the angiographic information was abundant and adequate in more than 90%, of the patients, the primary factual base of our analysis was angiographic. The ultimate proof of structural changes, however, are the gross and microscopic anatomic findings seen in the grafts themselves. However, since recovered graft material, because of obvious practical exigencies, was relatively scarce, it was necessary to identify, in the first phase of study, the important angiographic changes in the voluminous roentgen material (Table 8) and then find their expression, as the second phase of the study, in recovered specimens by comparing the anatomic findings with the recorded angiographic appearances. A sufficient amount of graft material was obtained to make such a retrospective interpretation highly reliable.

TABLE 2. *F-P Venous Autografts for Occlusive Disease Immediate Results by Severity of Disease*

Grade	Total No.	Open No.	Open %	Closed No.	Closed %	Amputation No.	Amputation %	Op. Mort. No.	Op. Mort. %
I	101	81	80.2	20	19.8	0	0	0	0
II	78	56	71.8	14	17.9	6	7.7	2	2.6
III	137	104	75.9	14	10.2	13	9.5	6	4.4
Total	316	241	76.3	48	15.2	19	6.0	8	2.5

TABLE 3. *241 Femoro-popliteal Venous Autografts for Occlusive Disease. Late Cumulative Patency Rates*

P.O. Length of Observation (Years)	No. of Grafts Total	No. of Grafts Open	% Cumul. Patency	No. of Deaths during Year of Observation	Cumulative no. of Patients Dead
1	241	215	89.2	18	18
2	208	177	85.1	15	33
3	177	138	78.0	26	59
4	139	100	71.9	8	67
5	116	74	63.8	9	76
6	95	51	53.7	5	81
7	75	38	50.7	6	87
8	59	28	47.5	1	88
9	45	20	44.5	2	90
10	25	11	44.0	2	92
11	9	2	22.2	0	92
12	5	1	20.0	0	92

The recovered graft material came from two basically different sources (Table 9). Eight grafts were recovered from patients' extremities who had died of various unrelated causes. In the remaining cases various portions of the graft were recovered at the time of surgical correction of some angiographically recognized abnormality. The recovered graft material was photographed, fixed for histologic studies, and stained with Gomori trichrome technic, hematoxylin-eosin, and orcein.

Results

ANGIOGRAPHIC FINDINGS

Types of Lesions (Table 8, Fig. 2). Eight types of morphological alterations could be recognized in the analysis of the extensive angiographic material.

The most common change was a wavy narrowing of the lumen, interpreted as intimal thickening (Fig. 3). Generally, this occurred along fairly extensive sections of the graft, occasionally involving the entire graft. The lesion was reminiscent of the fibrin deposition seen

TABLE 4. *48 Femoro-infrapopliteal Venous Autografts for Occlusive Disease Late Cumulative Patency Rates*

P.O. Length of Observation (Years)	No. of Grafts Total	No. of Grafts Open	% Cumul. Patency	No. of Deaths during Year of Observation	Cumulative no. of Patients Dead
1	48	35	72.9	6	6
2	33	19	57.6	2	8
3	13	7	53.8	0	8
4	5	4	80.0	1	9
5	3	2	66.7	0	9
6	2	1	50.0	0	9
7	1	1	100.0	0	9

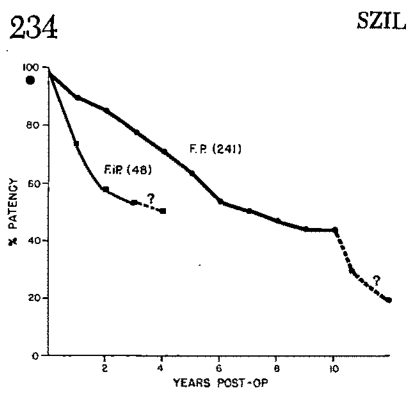


FIG. 1. Cumulative late patency rates of femoro-popliteal and femoro-infrapopliteal venous autografts.

TABLE 5. *Length of Observation and Number of Angiographic Examination. Lower Limb Venous Autografts*

Length of Observ. (Yrs.)	No. of Angiograms 1	2–3	4–4	6–7	>7	Totals
<1	83	12	0	0	0	95
1–2	8	54	1	0	0	63
3–4	1	34	8	1	0	44
5–6	0	23	8	1	1	33
7–8	1	7	4	1	0	13
>8	0	5	4	3	0	12
Total	93	135	25	6	1	260

in femoro-popliteal plastic prostheses,[25] but of a lesser degree, and appeared to be slower in development and progression. As will be pointed out presently, the corresponding pathologic change assumed two forms: true subendothelial hypertrophy and intimal clot layering.

Atherosclerosis, the second most common involvement among the structural deteriorations, was seen in 7.7% of the cases (Figs. 4–6 and C 10, C 11). The angiographic appearance consisted of an irregularity of the luminal surface, often associated with local dilatation of mild degree. In more advanced instances the irregular luminal outline assumed the morphological characteristics seen in atherosclerotic arteries: the hunchback contour of a typical atheroma.

Normal venous valve leaflets are often detectable in angiograms of vein grafts in the form of a cone-shaped hairline filling defect; these lead to no loss of lumen. The *fibrotic* valve, on the contrary, is an abnormal structure that does not assume the desired flat position when the vein graft is placed *in situ* and the blood is allowed to flow along the inverted valve leaflets. A sharply defined short-segment narrowing of the lumen is the result, usually in the midshaft of the graft, in which the valves are more closely spaced (Fig. 7).

The so-called *traumatic stenosis* anatomically consists of a fibrotic thickening of the wall which reduces the size of the lumen (Fig. 8). The designation implies trauma as the etiological agent but the evidence for this is not entirely secure. The defect occurs usually in a para-anastomotic position where a holding clamp is usually applied to the graft during placement of the anastomotic suture line. This topographic association between the site of a clamp and the appearance of a fibrotic stenosis strongly suggests that the cause of fibrosis is instrumental trauma to the vein wall.

Suture stenosis is perhaps the most obvious of these defects. It is the result of sutures applied too closely during ligation of the tributaries of the saphenous vein. It appears in the angiograms as a sharply localized stenotic ring.

Aneurysmal dilatation is a readily recognizable abnormality consisting of an abrupt increase in the diameter of the graft, the dilatation being usually fusiform. More uncommonly, the increase in diameter may be saccular and multiple. In all the cases that we were able to verify by anatomic examination, the dilatation was accompanied by atherosclerotic changes (Fig. 5), but the possibility remains that nonatherosclerotic dilatation may also occur as the result of some intrinsic local structural deficiency.

Two other abnormalities (not illustrated in Fig. 2) can be recognized in angiograms: an excessively long venous

TABLE 6. *Femoro-popliteal Venous Autografts As Arterial Bypasses Distribution of Maximum Periods of Follow-up Observation*

Length of Follow-up (Yrs.)	Clinical No. of Cases			Angiographic No. of Cases		
1	36			94		
2	31			27		
3	41			24		
4	21			19		
5	22			17		
6	23			14		
7	23		174(72.2%)	7		99(45.0%)
8	10	112(46.5%)		6	56(25.4%)	
9	18			5		
10	13			6		
>10	3			1		
	241			220		

stump at the ligated points of the tributaries, and an anatomical variation in the course of the greater saphenous vein just above the knee, often called "loop formation." These abnormalities do not ordinarily constitute a threat to the patency of the graft.

Time of Onset. In determining the time of onset of changes seen in angiograms, one encounters serious difficulties. In clinical material of the type here discussed, it is impossible to present a sequential series of angiograms so spaced as to give the optimum information necessary to determine the onset of a given structural change. Nevertheless, a sufficient number of patients underwent angiographic examinations at appropriate intervals to permit a close approximation of the actual points in time marking the onset of the alterations (Table 8). The time of onset of these changes showed variations that were consistent with the pathologic characteristics of the lesions. Atherosclerosis and aneurysmal dilatation appeared rather late (45 and 20 months postoperatively) as one would expect from the long period of time necessary for the evolution of these structural abnormalities. Suture stenosis, which, of course, has a practically instantaneous onset, was detected the earliest in the entire group. Fibrotic stenosis and intimal thickening occupied intermediate positions on the time scale.

The Degree of Severity of Lesions. The degree of severity of the changes must be judged on an arbitrary scale. Since there are no available absolute measuring standards, this does not detract from the value of the classification. Moreover, the degree of severity leaned toward underestimation rather than overestimation of the particular change in question. Whenever a doubtful early change was noted, it was disregarded unless a second angiographic examination confirmed its presence. On this scale, about one-third of all the changes noted were advanced and about two-thirds were early. The degree of involvement had an expected correlation with the type of lesion. Owing to their anatomic characteristics, some of the lesions were easier to recognize early in their evolution. Other lesions progressed slowly and thus recognition was delayed. Atherosclerosis, in particular, had to be moderately to markedly advanced before it could become recognizable in angiograms.

Progression of the Lesion. Ideally, the recognition of progression of a morphological change in the graft should be based on inspection of serial angiograms over a relatively protracted time scale. For the reasons already mentioned, in a clinical study including humans, this plan is not practicable. To reconcile the demands of accuracy with the exigencies of clinical practice, the following definition of progression was adopted: (1) Worsening of the lesion in at least two consecutive angiograms; (2) the appearance of a lesion after one or more normal

TABLE 7. *Femoro-infrapopliteal Venous Autografts as Arterial Bypasses*
Distribution of Maximum Periods of Follow-up Observations

Length of Follow-up (Yrs.)	Clinical No. of Cases	Angiographic No. of Cases
1	16 (33.3%)	23 (57.5%)
2	20 (41.7%)	14 (35.0%)
3	7	1
4	2 }12(25.0%)	0 }3(7.5%)
5	1	1
6	2	1
	48	40

TABLE 8. *Structural Changes in 220 Femoro-popliteal and 40 Femoro-infrapopliteal Venous Autografts Seen in Postoperative Angiograms*

		Time of Onset (Mos.)		Degree of Severity			Cases Showing		Ultimate Fate of Lesion: Observed		Ultimate Fate of Lesion: Reoperated	
Type of Lesion	Total Number	Range	Mean	+1	+2	+3	Progr* No. %	No Progr No. %	Open No. %	Closed No. %	Open No. %	Closed No. %
Intimal Thickening	21	(6–48)	16.2	16	5	0	14(66.6)	7(33.3)	15(75.0)	5(25.0)	1(All)	0(—)
Atherosclerosis	20	(6–70)	45.2	9	5	6	19(95.0)	1(5.0)	12(92.3)	1(7.7)	7(All)	0(—)
Fibrotic Valve	15	(6–60)	14.0	11	1	3	11(73.3)	4(26.7)	4(36.4)	7(63.6)	4(All)	0(—)
Fibrotic Stenosis	11	(6–60)	19.1	6	5	0	10(90.9)	1(9.1)	1(11.1)	8(88.9)	2(All)	0(—)
Suture Stenosis	8	(6–24)	9.0	7	1	0	6(75.0)	2(25.0)	3(37.5)	5(62.5)	0(—)	0(—)
Aneurysmal Dilatation	10	(6–80)	28.0	7	1	2	5(50.0)	5(50.0)	9(90.0)	1(10.0)	0(—)	0(—)
Total	85	(6–80)	23.9	56	18	11	65(76.5)	20(23.5)	44(62.0)	27(38.0)	14(100)	0(—)

* Progression: (1) At least two consecutive angiograms showing worsening of lesion; (2) The appearance of a lesion after one or more normal angiograms; and (3) Lesion seen in an angiogram followed by closure of graft.

Note: Loop-formation (2 cases) and excessively long stumps of tributaries (2 cases), not being intrinsic, are not included.

TABLE 9. *Femoro-popliteal and Femoro-infra-popliteal Venous Autografts. Graft Material Recovered in Part or in Whole*

					Structural Changes					
Case	Site	Months of Implantation	Length (cm)	Source of Recovery	Athero-sclerosis	Fibrotic Valve	Fibrotic Stenosis	Intimal Thickening	Multiple	"Normal"
1	F-P	44	whole	Autopsy	+					
2	F-P	31	whole	Autopsy						+
3	F-iP	13	whole	Autopsy				+		
4	F-P	58	whole	Autopsy	+					
5	F-P	63	whole	Autopsy					Atherosclerosis with Dilatation	
6	F-P	90	whole	Autopsy			+			
7	F-P	14	whole	Autopsy						+
8	F-P	10	whole	Autopsy	+					
9	F-iP	16	30	Surgical				+		
10	F-P	59	25	Surgical					Atherosclerosis with Dilatation	
11	F-P	78	10	Surgical					Atherosclerosis with Traumatic stenosis	
12	F-iP	6	10	Surgical				+		
13	F-iP	10	5	Surgical				+		
14	F-P	20	3	Surgical		+				
15	F-P	13	1	Surgical		+				
16	F-P	96	Biopsy	Surgical	+					
17	F-F	7	Biopsy	Surgical			+			
18	F-P	59	Biopsy	Surgical					Atherosclerosis with Fibrotic Valve	
19	F-P	19	Biopsy	Surgical		+				
20	F-P	36	Biopsy	Surgical			+			
21	F-P	15	Biopsy	Surgical			+			

angiograms; and (3) the appearance of a lesion in an angiogram followed by closure of the graft. The only conjectural part of this definition deals with the establishment of progression after a single angiogram followed by closure of the graft. This part of the definition presumes that no other cause could be detected for eventual loss of patency in the graft. With this qualification the definition has an acceptable degree of clinical accuracy.

In the terms defined, all the angiographic lesions showed progression, albeit with some variations in the rate of progression. Progression was most consistent in atherosclerosis and traumatic fibrous stenosis. Aneurysmal dilation appeared to be the least likely to progress but this may have been partly illusory since the pathologic characteristic of the lesion retards its evolution and it seldom leads to thrombosis even in the late states.

Ultimate Fate. The ultimate fate of these alterations was in keeping with the trend observed in their progression. This trend, of course, is seen only in those lesions that were not subject to surgical correction. In this group, closure as an end result was particularly prevalent in all the various forms of stenotic changes. Atherosclerosis, on the contrary, was slow to lead to occlusion. The outcome of the evolution of the lesions was markedly and favorably influenced by reoperation. The results of operation were invariably excellent and no graft, in which a defect had been surgically corrected, occluded during the time of this study. As will be pointed out later, due to their pathologic characteristics some lesions are less suited for surgical repair, whereas others are eminently suitable for correction. Short segment stenotic lesions promise outstandingly good results.

ANATOMIC FINDINGS

Source of Material. The anatomic study of autogenous vein grafts has been very seriously hampered by the difficulties encountered in their recovery after death of the patients. The many practical reasons for this difficulty are obvious. Amputation specimens of grafts that have failed are much easier to come by but, unfortunately, very severe time limitations must be observed in the evaluation of grafts recovered in this manner. Very likely, after 3 or 4 weeks the histologic findings are impossible to interpret with accuracy and even in earlier specimens great caution must be exercised in the analysis of the findings. The operating room is an excellent source of smaller pieces of vein material. This form of acquisition, however, introduces an obvious bias in the study of the natural behavior of these grafts since all the surgically available specimens have been preselected, that is, they have a recognized abnormality for which the surgical procedure is undertaken. When actual resection of an implant is not necessary in course of a surgical procedure, biopsy also may prove very useful. Nor must one underestimate the value of careful inspection of the graft during surgical exploration, particularly when the inner aspect of the graft is carefully exposed.

We have succeeded in collecting anatomic information on 21 autogenous vein specimens. Seventeen of these specimens came from femoro-popliteal grafts and four from femoro-infrapopliteal grafts. The length of the recovered specimen varied from complete length to shorter segments 1 to 30 cm. in size, and to small biopsy specimens. The average period of implantation was 3 years, ranging from 6 months to 8 years. Eight of the specimens, representing complete grafts, were obtained at autopsy and 13 were recovered at operative interventions.

Comparative Significance of Anatomic Findings.—From the point of view of the inherent capability of venous autografts to serve as effective arterial blood conduits (the assessment of which is the principal goal of this study) one must assign different orders of importance to anatomic changes that are due to extrinsic causes and to those that are inherent in the histologic reaction of the graft to its post-implantation environment. With very few exceptions, the lesions of extrinsic etiology are confined to small areas with extensive intervening tissue segments that show no deviation from the normal process of incorporation. In cases of fibrotic stenosis due to trauma, fibrotic valve cusps, or suture stenosis, nearly the whole graft—aside from the site of the lesion—may be free of morbid change. Although, if uncorrected, they may cause graft failure, these local abnormalities, since they can be prevented or corrected, are not among the factors that determine the ultimate intrinsic serviceability of the graft. The lesions that are all-important with respect to structural durability are the intrinsic lesions, namely, atherosclerosis, intimal thickening, and aneurysmal dilatation (the latter often being a manifestation of

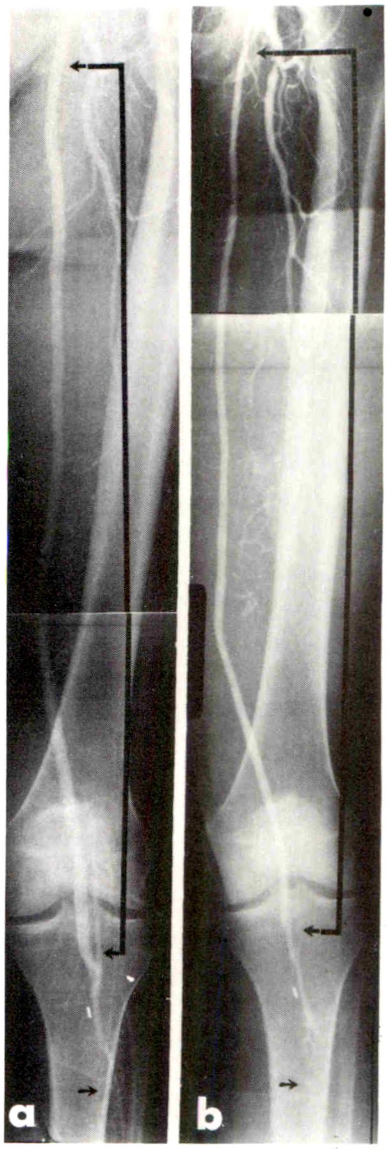
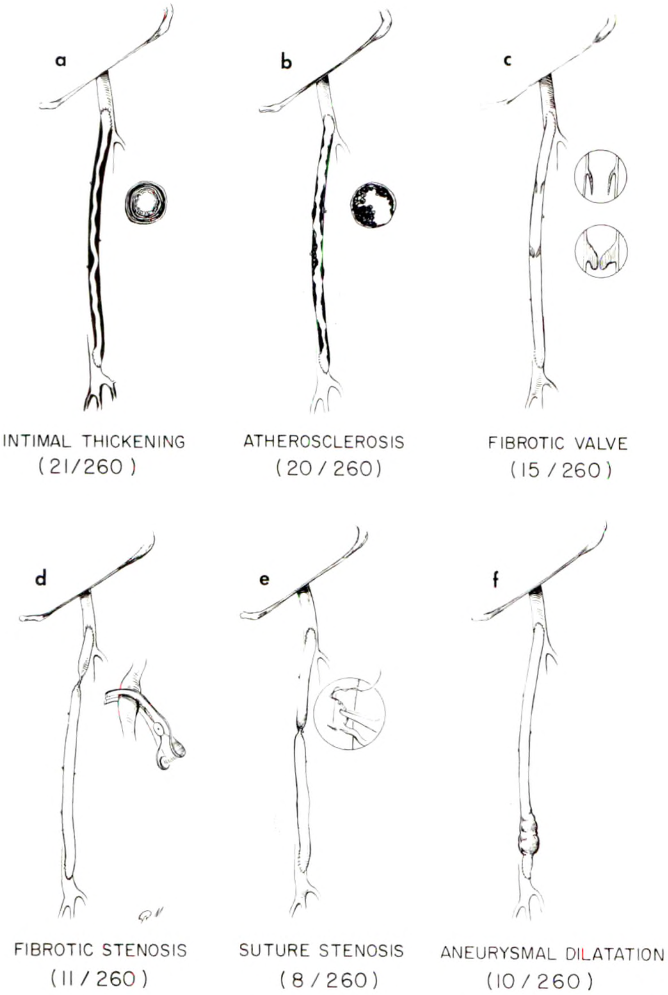


FIG. 3. Angiograms of femoro-popliteal autogenous vein bypass (a) two weeks and (b) 19 months postoperatively. Stream-line-like narrowing of the lumen along most of the graft due, in this case, to deposition of fibrin clots on the intimal surface (layering). See also Figs. C7 and C8 for corresponding microscopic changes.



INTIMAL THICKENING (21/260) ATHEROSCLEROSIS (20/260) FIBROTIC VALVE (15/260)

FIBROTIC STENOSIS (11/260) SUTURE STENOSIS (8/260) ANEURYSMAL DILATATION (10/260)

FIG. 2. Schematic representation of morphologic changes of venous autografts seen in angiograms.

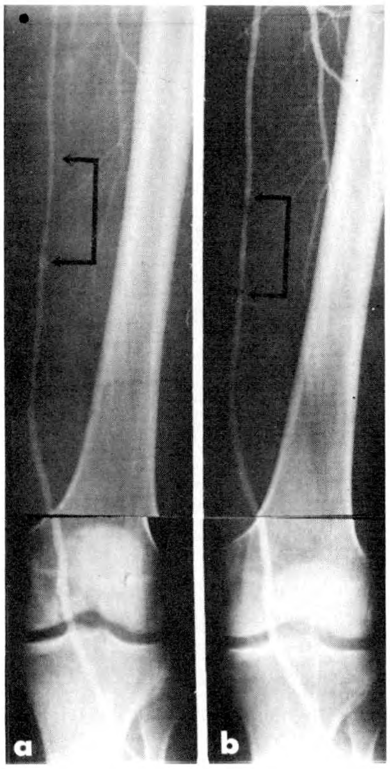


FIG. 4. Angiogram of femoro-popliteal venous autograft with atherosclerosis (a) three months and (b) 4.5 years after the primary operation. See also Figs. C10, C11, C12 from the same case.

atherosclerosis); all these alterations tend to be diffuse.

When calculating the frequency of the anatomic abnormalities, another restriction must be kept in mind. Because of the statistical bias inevitable in the selection of cases for surgical correction, the incidence of the anatomic changes of importance for the ultimate fate of the graft should be established on grounds of the findings in autopsy rather than in operative specimens.

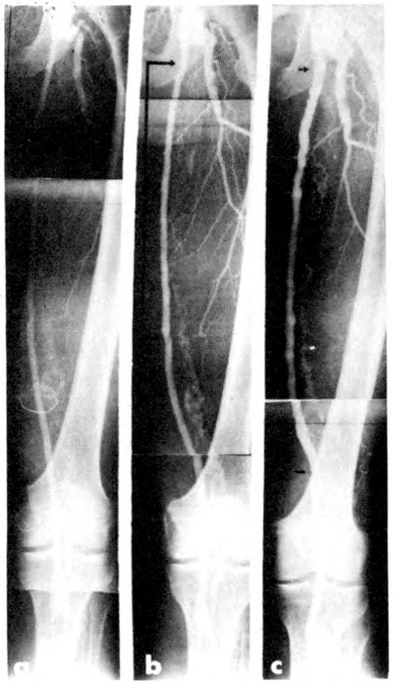


FIG. 5. Angiograms of femoro-popliteal venous autograft showing the evolution of atherosclerotic changes (b) 2 years and (c) 5 years postoperatively. See also Fig. C13 from the same case.

Among the autopsy specimens examined in this investigation, two were normal, one presented a very small area of mild traumatic stenosis, three showed diffuse atherosclerosis of modest degree, one showed atherosclerosis with local dilatation, and one showed diffuse intimal hypertrophy.

Gross and Microscopic Anatomy of Normal Graft Incorporation.—The concept of normality in judging the process of incorporation of a graft is defined as that anatomic picture that does not lead to structural changes unfavorable to normal function. Grossly, such grafts resemble to varying degrees the macroscopic appearances of a normal saphenous vein (Fig. C3). The only deviation from the appearance of an intact healthy saphenous vein that the naked eye can detect is the thickness of the wall which is usually increased. Microscopically a rather characteristic set of histologic features subsume this "normal" appearance (see below).

The microscopic features affect all three regions of the wall: intima, media, and adventitia. The intensity of change varies from layer to layer, and also from one region of the vein to another. Even grafts that are in-

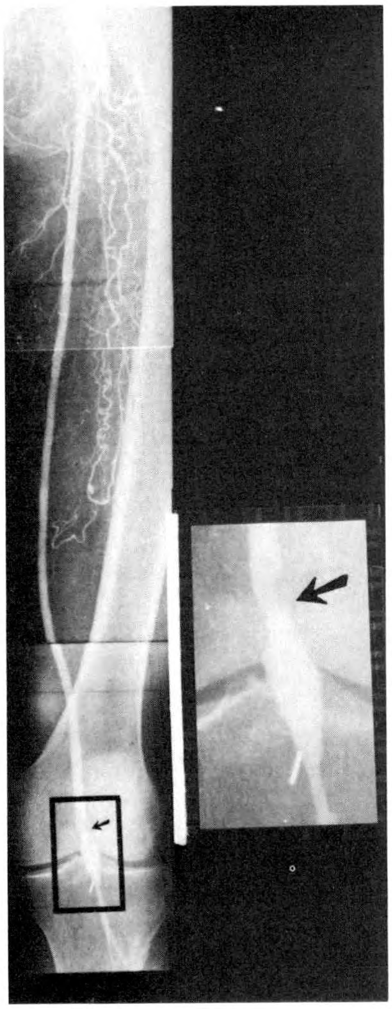


FIG. 6. Angiographic appearance of sharply localized atheroma four years, 9 months after femoro-popliteal autogenous vein bypass. Further findings of the same case are shown in Figs. C14, C15, and C16.

volved in atherosclerotic changes may show segments that appear to be normal.

To gain a clear comprehension of the changes of incorporation, one must recall the *normal histological appearances of the saphenous vein* (Fig. C1).

The histologic features of the (greater) saphenous vein are unique among venous structures. Because of its anatomic location that creates hemodynamic stresses unusual for a vein, it is thick-walled and very rich in smooth muscle and elastic tissue elements. The smooth muscle fibers are arranged in an inner longitudinal and an outer circular layer, extending through the entire thickness of the wall except the immediate subendothelial layer of collagen tissue and the outer portions of the loose connective tissue of the adventitia. In between the smooth muscle fibers of the media collagen fibers are interspersed forming about 20 percent of the total tissue mass. The intimal surface is bounded by a single layer of flat endothelial cells that rest on a narrow band of collagen tissue. As already mentioned, smooth muscle elements intrude to the very level of the subendothelial collagen tissue. The subendothelial collagen band and the intermingled smooth muscle elements, which at this level form scattered delicate bundles, are usually de-

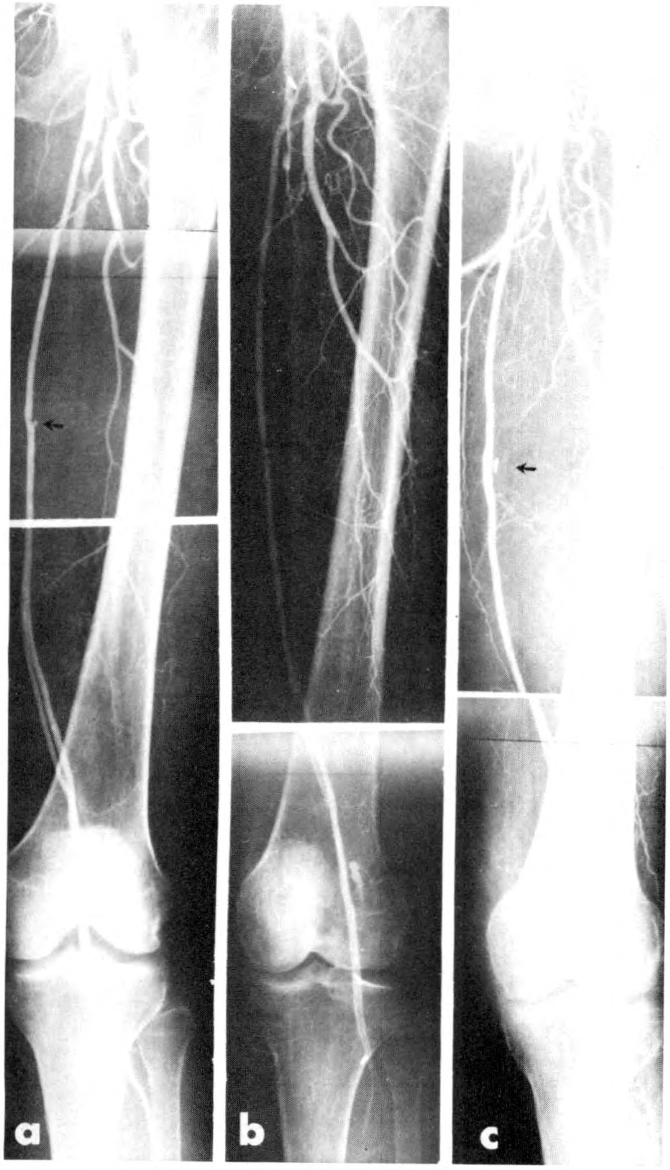


FIG. 7. Angiograms of femoro-popliteal venous autograft (a) 2 weeks and (b) 19 months postoperatively, and (c) 2 weeks after secondary repair. Arrow points to venous valve with thick fibrous cusps that have caused a well-marked stenosis. Clip (in c) marks site of repair.

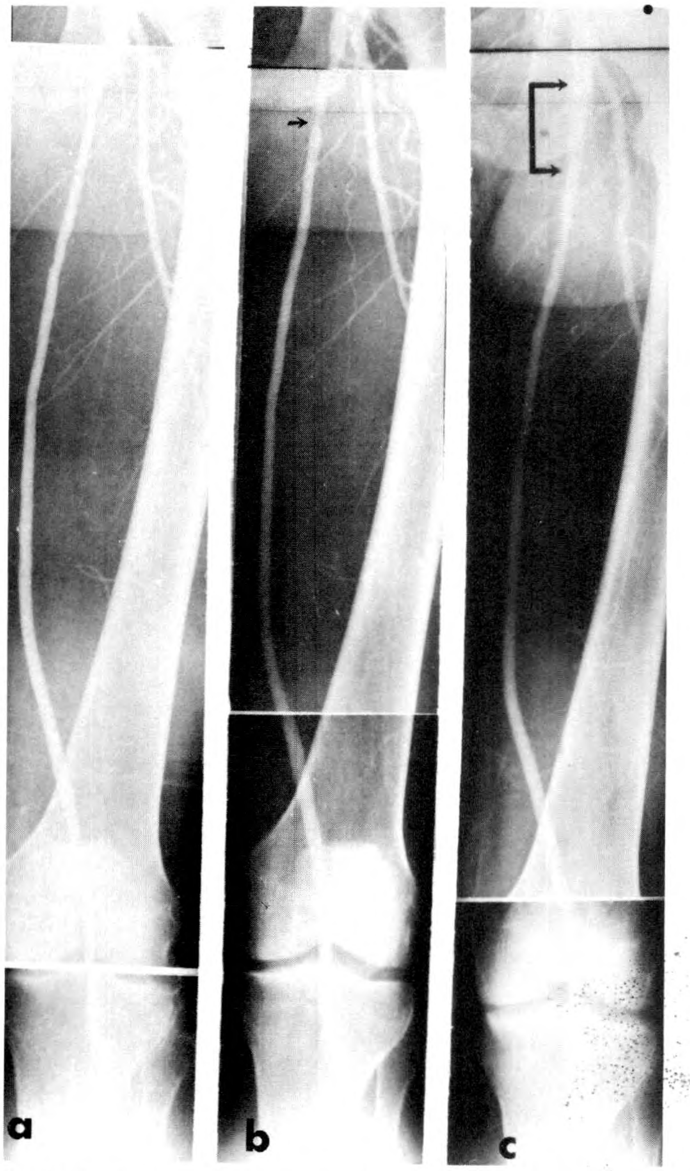


FIG. 8. Angiograms of femoro-popliteal venous autograft showing fibrotic (traumatic) stenosis (a) 3 months after primary operation (the lesion is not yet recognizable), (b) 15 months after the primary operation, and (c) 2 weeks after secondary correction.

marcated from the media by an elastic lamina that often forms a continuous circular layer, much as the inner elastic lamina of a muscular artery. The adventitia, in a strict sense is not an intrinsic part of the vein wall. It is usually sharply marked off from the tightly structured circular muscle layer of the media by elements of loose composition that are intermingled with irregularly scattered elastic and, to a less extent, smooth muscle fibers. Nutrient blood vessels are fairly abundant in the adventitia but penetrate only to the outer layers of the media.

The most striking change in the process of *normal incorporation* occurs in the smooth muscle elements (Figs. C2, C4, C16). From the earliest to the latest observations covering a span of time of from 6 to 96 months of implantation, a diminution of the smooth muscle fibers is evident. The proportion of the smooth muscle elements preserved varies and is difficult to correlate with the only readily definable factor influencing it: the length of implantation. Some late specimens may have occasionally more smooth muscle preserved than some earlier ones, very likely because of the existence of a host of unrecognizable factors that may hasten the devitalization of the smooth muscle fibers. (It is known, for instance, that the length of warm ischemia time after removal has distinct effects on the survival of smooth muscle tissue. A similar role must be assigned to mechanical trauma, ambient hydrogen ion concentration, and type of preserving solution.) Upon the whole, however, the longer the implantation the fewer the smooth muscle elements. It should be also noted that at times the persistence of smooth muscle elements is confined to two sharply defined regions: the immediate subendothelial and the outer medial regions, a phenomenon that may be related to the availability of blood supply. As the smooth muscle fibers disappear, they are replaced by collagen tissue which thus tends to form an increasingly more prominent proportion of the substance of the venous wall as the time of implantation lengthens. All the specimens we examined, however, had retained some, usually significant, amounts of smooth muscle tissue. (These observations are in accord with those of Wyatt on experimental preparations.[19,28])

The intimal changes seen after implantation, although of nearly universal occurrence, must be regarded as an abnormal histologic event and will be described under the heading of morbid anatomy.

The adventitia displays quite consistent and characteristic modifications of its structure. There is an ingrowth of vascular elements usually limited to the adventitia and outer media. The elastic elements in the adventitia are usually hypertrophic, and at times markedly so.

Gross and Microscopic Anatomy of Morbid Changes.—As mentioned earlier, the histologic alterations that have the decisive role in determining the ultimate functional fate of the graft are intimal thickening and atherosclerotic degeneration. Both are diffuse processes (though they often show regional accentuation) and both are very common. In fact, some degree of intimal thickening is present in all grafts, and it is discussed under the heading of morbid anatomy mainly because it represents a tissue change adverse to continued normal function.

The process of intimal thickening, a rather inelegant but necessary designation, is a complex one. At least two distinct pathological processes appear to underlie the changes that are described by this term. One process is the result of the response of the subendothelial venous wall—the subendothelial collagen and smooth muscle fibers—to the altered hemodynamic conditions in the lumen. It is manifested by an overgrowth of the subendothelial elements, mainly the subendothelial smooth muscle fibers (Figs. C9, C16). This reaction to the increased intraluminal pressure was seen in every specimen examined except those in which its place was taken by a second variant of intimal thickening: the so-called fibrin layering. Fibrin layering is a process of deposition and organization of successive films of fibrin clot on the intimal surface when the restricted outflow tract or turbulent flow at the distal anastomosis reduces the velocity of blood flow (Figs. C7, C8). Subendothelial hypertrophy is a very graded and slow process and is much less readily discernible in angiograms than fibrin layering, which progresses rather rapidly. Both of these changes are a threat to the continued function of the implant, but the danger of closure from layering is patently more serious.

The atherosclerotic changes are both grossly (Figs. 11 and C14) and microscopically (Figs. C12, C13, and C15) quite amazingly similar to those seen in arteries. Early fibrotic plaques with the beginning of lipid infiltration mark the earliest phase. The changes may be followed sequentially to the development of the entire atherosclerotic complex with its amorphous necrotic center, underlying collagen base, and ulcerated intimal surface, usually covered by a layer of fibrin clot. These alterations are usually diffuse, but occasionally may be sharply localized perhaps due to some local mechanical factor. There appears to be a time dependence in the evolution of atherosclerotic changes. The older the specimen the more likely to show the change and the more severe the degree of change. About 80 percent of the implants examined two years or more after implantation showed evidence of atherosclerosis.

The Possible Role of Atherogenic Factors.—Since systemic veins show an almost absolute resistance to the development of atherosclerosis, the question naturally arises whether the relatively high incidence of atheromatous change in the veins used as arterial conduits in the lower extremity might not be the result of the presence of particularly strong atherogenic factors in the patients. We tested this assumption by comparing the incidence of certain atherogenic factors in the two groups of patients—one with and the other without atherosclerotic changes in their grafts. A summary of these data is displayed in Table 10. In the first columns are listed the selected atherogenic factors and in the next two columns their incidence in the two groups being compared. It is readily seen that no significant differences were demonstrated.

TABLE 10. *Incidence of Atherogenic Factors in 22 Patients with and 244 Patients without Atheromatous Graft Changes*

Atherogenic Factor	Cases with the Atherogenic Factor Present			
	(A) Grafts with Atherosclerosis		(B) Grafts without Atherosclerosis	
	No.*	%	No.	%
Males	18/22	81.8	185/244	75.8
Total Lipids >900 mg./100 ml.	7/22	31.8	55/153	35.0
Cholesterol >300 mg./100 ml.	2/21	9.5	14/190	7.4
Triglycerides >140 mg./100 ml.	8/14	57.2	47/71	66.2
Cigarettes >1 pack/day	12/21	57.1	101/237	42.6
Associated Diabetes	11/22	50.0	93/244	38.1
Systemic** Involvement by Atherosclerosis	14/22	63.7	179/243	73.7

* Denominator: Number of patients for whom the presence of the named factor was determined.

Numerator: Number of patients in whom the factor was in abnormal range.

** More than two organ systems involved.

Note: Range of ages: Group A = 50–75 years; Group B = 28–84 years.

Mean of ages Group A = 61.1 years; Group B = 63.1 years.

Comments

Validity of Angiographic Interpretation. Throughout the exposition of this study, morphological changes in the graft were interchangeably expressed in terms of angiography and anatomic description. The question is justified whether this process of equating angiographic shadows with changes that are structural and tridimensional is valid. The answer to this question must be given in terms of the evolution of this process of interpretation. When these angiographic findings were first encountered they were merely recognized as some sort of morphological defect, but no anatomic meaning was attached to them. As either postmortem or intraoperative exploration showed the nature of the lesions, certain angiographic appearances assumed anatomical significance. With increasing experience the interpretation became secure enough to permit extrapolation from angiographic shadow to anatomic structure. We have repeatedly observed morphological lesions that were first described in speculative anatomic terms only to be proven later to correspond precisely to the supposition of the tentative diagnosis. It seems justified to say that this process has reached a clinically acceptable degree of accuracy.

Assessment of the Value of Autogenous Vein Grafts. In any attempt to evaluate the worth of saphenous vein grafts in the lower extremity, a clear distinction must be made between the tissue acceptance of these autografts and their functional usefulness. Tissue acceptance is almost absolute. No histologic changes associated with homogeneic implants or foreign body implants can ever be observed. Not only is there no trace of rejection, but, in addition, the anatomic structure of the vein shows some changes that favor durability; the hypertrophy and hyperplasia of the connective tissue and elastic tissue elements of the adventitia are particularly significant in this respect. A particularly fortunate aspect of the incorporation of the graft is the generally good preservation of the smooth muscle elements. As will be pointed out below, the frequent absence of a normal intima and the changes in the subendothelial elements when an intima is preserved undoubtedly constitute a serious deficiency but their significance, under normal hemodynamic conditions, is a long-term one.

In regard to the functional value, it must be considered under two aspects. The potential causes of graft deterioration appear alarmingly common if one considers the crude statistical incidence (32.7%) of the lesions observed. From this observation alone one would predict that about one-third of the implants will develop serious defects most of which would threaten the long-term function of the graft. As has already been mentioned briefly, however, about one-half of the potential defects are preventable or remediable (if detected early enough). Fastidious technic should avoid traumatic and suture fibrosis and, if recognized promptly, fibrotic valve stenosis should be readily corrected.

There still remain, however, the intrinsic lesions to which the graft is susceptible, namely, atheroclerosis and intimal thickening. Atherosclerosis in particular appears to be an inevitable ultimate abnormality that overtakes these implants commonly, and perhaps even universally, if they stay *in situ* long enough.[26,27] Fortunately, atherosclerosis evolves very slowly, taking 4 to 6 years for development to a threatening degree. Subendothelial hypertrophy is also a progressive alteration and it follows a similarly insidious course. Both subendothelial hypertrophy and mural layering are undoubtedly a major threat to patency whenever the distal hemodynamics are unsatisfactory. Under these conditions, apparently the same process is destined to occur in the autogenous vein graft as has been observed abundantly in synthetic femoro-popliteal prostheses but, fortunately, at a slower rate and less commonly.

Relevance to the Question of Pathogenesis of Atherosclerosis. The observations made on the atherosclerotic changes in these grafts have a particularly exciting theoretical implication. Since in the majority of the grafts with atherosclerosis no strong biochemical factor can be detected, the autogenous vein constitutes a good experimental model for testing the importance of hemodynamic factors in the causation of atherosclerosis. Since in the same individual a peripheral vein will be totally immune to the process of atherogenesis when it is under the hemodynamic conditions of the venous system, but becomes fairly readily involved in the atherosclerotic process when it is placed on the arterial side of the circuit, the conclusion is inescapable that the primary cause of the atherosclerotic involvement is hemodynamic.

Correlation with Coronary Surgery. Another interesting speculative aspect of these findings is their possible significance in the evaluation of the use of saphenous venous autografts in the aorto-coronary circuit. Considering the most important factors relevant to the longevity of the graft, the two clinical uses are readily comparable. The vein material is the same, the surgical technical steps are alike, and the hemodynamic factors are similar. The differences are mainly qualitative and relate to the blood pressure relationships, tissue environment and the distal hemodynamics. Unfortunately all the differences are in the disfavor of the aorto-coronary procedure. The arterial blood pressure is higher, the tissue bed in which the graft is placed is less receptive (less capable of creating a true environment for good incorporation of the graft which is partly without tissue support) and the arterial outflow circuit is greatly constricted. These considerations suggest that the same intrinsic structural lesions may be expected in the vein grafts used as aorto-coronary bypasses but possibly with an accelerated tempo of development. The sporadic reports on the anatomic changes in aorto-coronary venous autografts[11,13,14,16,17] strongly suggest that this assumption is correct.

The Question of Prophylaxis.—An analysis of the behavior of these grafts emphasizes the importance of certain sample prophylactic measures in our attempt to prolong their usefulness. The avoidance of trauma in freeing the vein graft is an obvious requirement. Less evident is the need for the reduction of the time interval during which the vein graft is deprived of its blood supply at normal temperature ("warm-ischemia time"). This need can be met by allowing blood flow to continue through the vein while it is being prepared and while its tributaries are being tied, and by placing it in a cold isotonic glucose solution at a pH near 7.0 while it is being stored before insertion. Very close postoperative observation of the grafts (preferably by angiography) for the earliest possible detection of changes that might be remediable also appears to be highly desirable.

FIG. C1. Normal greater saphenous vein. Transverse section. ×175. *Note:* In this and all following microscopic sections, the stain, unless otherwise noted, is by the Gomori trichrome method, and the intimal surface is directed to the right. In the Gomori trichrome technic collagen stains green or greenish blue (the more mature the collagen fiber, the deeper the greenish hue), smooth muscle red, fibrin red, and elastic tissue violet. The approximate boundaries of the layers of the wall are marked by short black bars. I = intima, M = media, A = adventitia.

FIG. C2. Greater saphenous vein after 31 months of implantation showing normal incorporation. ×130.

FIG. C3. Grossly normal greater saphenous vein recovered 90 months after implantation. Uppermost segment represents the region of proximal anastomosis.

FIG. C4. Microscopic section of graft in Fig. C3. *Left:* Gomori stain; *right:* Orcein elastica stain. ×28.

FIG. C5. Fibrotic valve cusps seen at surgical exposure.

FIG. C6. Microscopic section of fibrotic valve in Fig. C5. ×35.

FIG. C7. Microscopic section of greater saphenous vein recovered 16 months after implantation. Fresh fibrin clots on intimal surface overlying partly organized older fibrin layers of different ages. *Cf.* Fig. 3. ×70.

FIG. C8. Section of greater saphenous vein recovered 20 months after implantation. Intima consists principally of organized fibrin clot with minimal smooth muscle elements. A more mature variant of intimal fibrin layering seen in Fig. C7. *Cf.* Fig. 3. ×100.

FIG. C9. Microscopic section of greater saphenous vein 19 months after implantation. Marked subendothelial hypertrophy with abundant smooth muscle elements. ×63.

FIG. C10. Arteriogram of greater saphenous venous autograft in midthigh with superimposed graft specimen showing atherosclerosis, 78 months after implantation.

FIG. C11. Operating-room photograph. *At bottom:* diseased segment of venous autograft in midthigh (seen also in Fig. C10) exposed at time of replacement 78 months after implantation. *At top:* vein segment used for replacement.

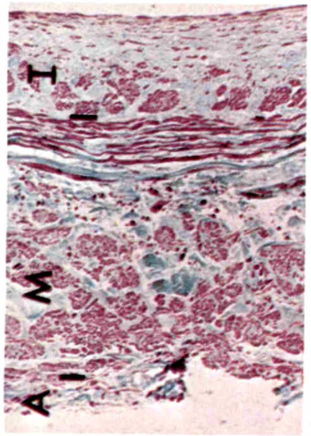
FIG. C12. Microscopic section of atheromatous lesion of diseased vein in Fig. C11. ×115.

FIG. C13. Microscopic section of ulcerated subintimal atheroma in greater saphenous venous autograft recovered 63 months after implantation. For angiographic appearance, see Fig. 5. ×35.

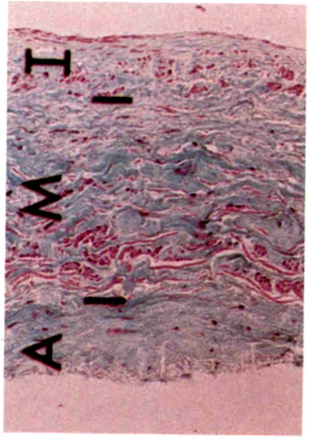
FIG. C14. Atheromatous intimal ulceration localized to vicinity of distal anastomosis in a greater saphenous venous autograft 58 months after implantation. Postmortem specimen superimposed on arteriogram. For antemortem angiogram, see Fig. 6.

FIG. C15. Microscopic section of atheromatous ulceration in Fig. C14. ×28.

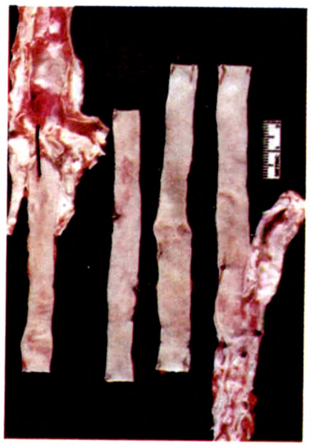
FIG. C16. Microscopic section from midshaft of graft in Fig. C14 showing normal incorporation. (Intima thick and rich in smooth muscle fibers; media markedly narrowed, with few smooth muscle elements; adventitia normal.) ×35.



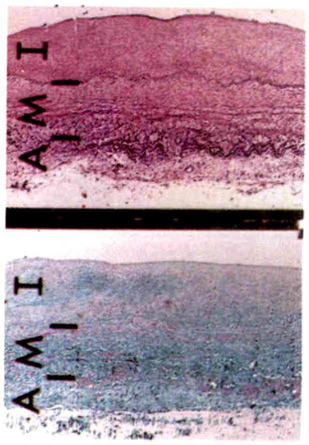
C1



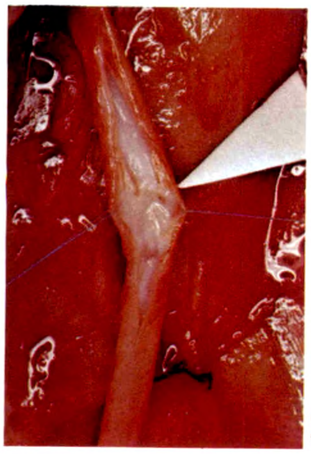
C2



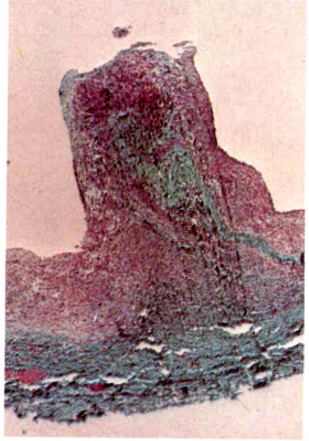
C3



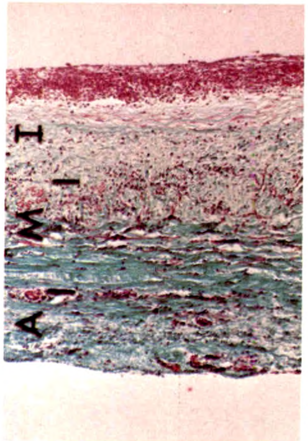
C4



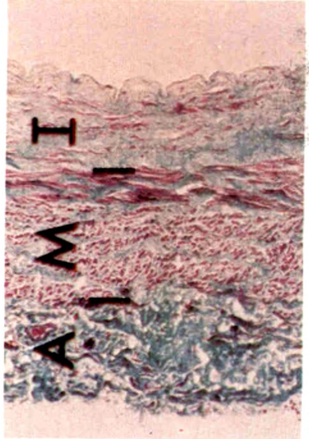
C5



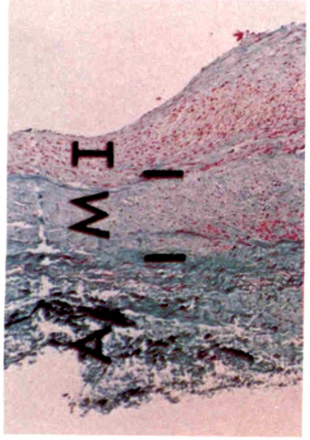
C6



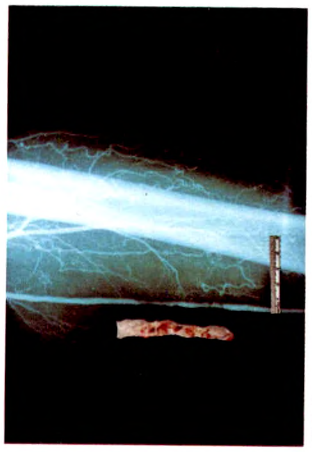
C7



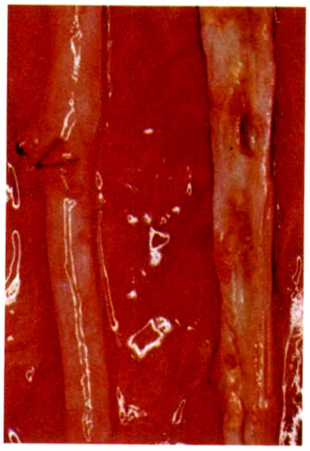
C8



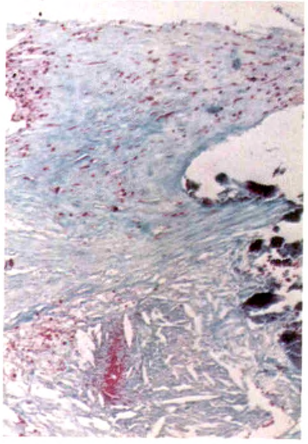
C9



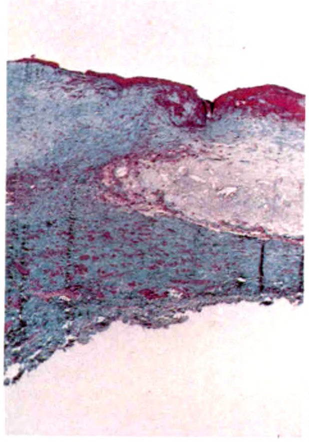
C10



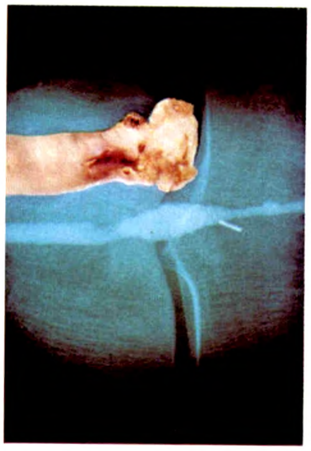
C11



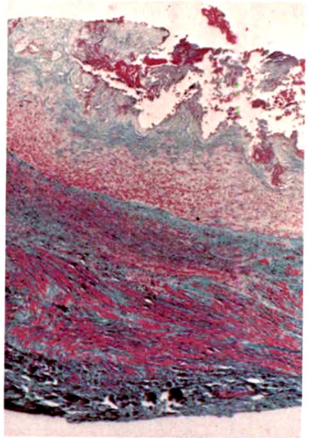
C12



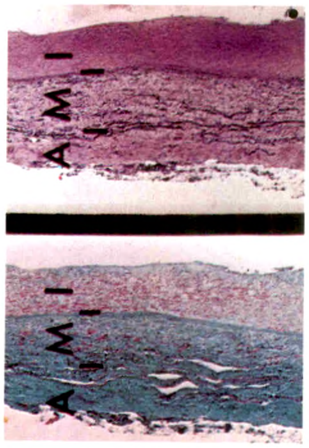
C13



C14



C15



C16

Conclusions

Autogenous vein transplants used as arterial substitutes in the femoro-popliteal and femoro-infrapopliteal regions shown excellent tissue acceptance, and the femoropopliteal grafts yield good functional results. After 5 years of observation, 64%, and after 10 years of observation, 44% of the femoro-popliteal grafts appear structurally sound and functionally unimpaired.

Structural defects develop in 32.7 percent of the grafts as the result of technical mishaps (stenosis due to improper suturing and to instrumental trauma) and due to intrinsic tissue changes (subendothelial hypertrophy, layering of intimal thrombi, fibrosis of venous valves, and atherosclerosis). All of these changes are progressive and may lead to the loss of patency of the graft. Some of these can be avoided by greater care in technique and others can be corrected if discovered early. Atherosclerosis and intimal thickening (i.e., subendothelial hypertrophy and fibrin layering) are not remediable and will continue to be a major cause of loss of graft function.

References

1. Beebe, H. G., Clark, W. F. and DeWeese, J. A.: Atherosclerotic Change Occurring in an Autogenous Venous Arterial Graft. Arch. Surg., **101**:85, 1970.
2. Bolasny, B. L., Lanier, V. C., Younger, R. K. and Scott, H. W.: Comparison of Vein Grafts and Dacron Grafts in the Femoral and Iliac Arteries in Dogs on an Atherogenic Regimen. Surg. Forum, **20**:99, 1969.
3. Breslau, R. C. and DeWeese, J. A.: Successful Endophlebectomy of Autogenous Venous Bypass Graft. Ann. Surg., **162**:25, 1965.
4. Brody, W. R., Kosek, J. C., Angell, W. W. and Shumway, N. E.: Changes in Vein Grafts Following Aorto-coronary Bypass Induced by Pressure and Ischemia. J. Thorac. Cardiovasc. Surg., **64**:847, 1972.
5. Davison, E. D. and DePalma, R. G.: Atherosclerotic Aneurysm Occurring in an Autogenous Vein Graft. Am. J. Surg., **124**:112, 1972.
6. De La Rocha, A. G., Peixoto, R. S. and Baird, R. J.: Atherosclerosis and Aneurysm Formation in a Saphenous Vein-Graft. Brit. J. Surg., 60: January, 1973.
7. DeWeese, J. A. and Rob, C. G.: Autogenous Venous Bypass Grafts Five Years Later. Ann. Surg., **174**:346, 1971.
8. Downs, A. R.: Repair of Late Vein Graft Occlusions. Arch. Surg., **103**:639, 1971.
9. Downs, A. R. and Sinha, B. K.: Assessment of Reconstructive Procedures for Femoropopliteal Artery Occlusive Disease. Can. Med. Ass. J., **102**:141, 1970.
10. Ejrup, B., Hiertonn, T. and Moberg, A: Atheromatous Changes in Autogenous Venous Grafts. Acta Chir. Scand., **121**:211, 1961.
11. Flemma, R. J., Johnson, W. D., Lepley, D., Tector, A. J., Walker, J., Gale, J., Beddingfield, G. and Manley, J. D.: Late Results of Saphenous Vein Bypass Grafting for Myocardial Revascularization. Ann. Thorac. Surg., **14**:232, 1972.
12. Friedman, S. A., Cerruti, M. M. and Amadeo, B.: Spontaneous Necrosis of a Functioning Saphenous Vein Graft. Surgery, **66**:1022, 1969.
13. Grondin, C. M., Meere, C., Castonguay, Y., Lepage, G. and Grondin, P.: Progressive and Late Obstruction of an Aorto-Coronary Venous Bypass Graft. Circulation, **43**: 698, 1971.
14. Grondin, C. M., Castonguay, Y. R., Lepage, G., Meere, C. and Grondin, P.: Aortocoronary Bypass Grafts. Arch. Surg., **103**:535, 1971.
15. Haimovici, J. and Maier, N.: Experimental Canine Atherosclerosis in Autogenous Abdominal Aortic Grafts Implanted into the Jugular Vein. Ather., **13**:375, 1971.
16. Hamaker, W. R., Doyle, W. F., O'Connell, T. J. and Gomez, A. C.: Subintimal Obliterative Proliferation in Saphenous Vein Grafts. Ann. Thorac. Surg., **13**:488, 1972.
17. Johnson, W. D., Auer, J. E. and Tector, A. J.: Late Changes in Coronary Vein-Grafts. Am. J. Cardiol., **26**:640, 1970.
18. Katzadze, M. A. and Sapozhnikova, L. P.: On Changes in Endothelium of Autovenous Transplant After Its Grafting into Peripheral Arteries. Arkh. Anat., **57**:89, 1969. (In Russian. English Summary.)
19. McCabe, M., Cunningham, G. J., Wyatt, A. P., Rothnie, N. G. and Taylor, G. W.: A Histological and Histochemical Examination of Autogenous Vein Grafts. Brit. J. Surg., **54**: 147, 1967.
20. McNamara, J. J., Darling, R. C. and Linton, R. R.: Segmental Stenosis of Saphenous Vein Autografts. N. Engl. J. Med., **277**:290, 1967.
21. Ramirez, A. and Stallworth, J. M.: Long-term Behavior of Vein Grafts as Replacements for Arterial Segments within the Peritoneal Cavity. Surgery, **69**:832, 1971.
22. Scott, J. W., Morgan, C. V., Bolasny, B. L., Lanier, V. C., Younger, R. K. and Butts, W.: Experimental Atherosclerosis in Autogenous Venous Grafts. Arch. Surg., **101**:677, 1970.
23. Stein, A. A., Rosenblum, I. and Leather, R.: Intimal Sclerosis in Human Veins. Arch. Path., **31**:548, 1966.
24. Szilagyi, D. E., Smith, R. F., Macksood, A. J. and Eyler, W. R.: Abdominal Aortography: Its Value and Its Hazards. Arch. Surg., **85**:24, 1962.
25. Szilagyi, D. E., Smith, R. F., Elliott, J. P. and Allen, H. M.: The Long-Term Behavior of a Dacron Arterial Substitute: Clinical, Roentgenological, and Histological Correlations. Ann. Surg., **162**:453, 1965.
26. Szilagyi, D. E.: Discussion of DeWeese, J. A. and Rob, C. G.: Autogenous Venous Bypass Grafts Five Years Later. Ann. Surg., **174**:346, 1971.[7]
27. Szilagyi, D. E.: Discussion of Downs, A. R.: Repair of Late Vein Graft Occlusions. Arch. Surg., **103**:639, 1971.[8]
28. Wyatt, A. P., Rothnie, N. G. and Taylor, G. W.: The Vascularization of Vein Grafts. Brit. J. Surg., **51**: May, 1964.

Discussion

Dr. Jere W. Lord, Jr. (New York City): There are two points of many which Dr. Szilagyi made that I would like to comment upon. One is that most of us thought early and late failures in vein graft bypasses were due to technical operative errors, and more commonly, progression of the atherosclerotic process in the inflow tract above or in the outflow tract below.

Our experience in the last 3 years confirms his presentation. Our failures have usually been due to intrinsic diseases of the vein graft. Two conditions in particular should be mentioned. First, fusion of a venous valve. In reversed vein bypass grafts, one would think that they would always be flattened against the wall. In perhaps one or two per cent fusion takes place. The other condition is fibrotic stenosis of the intima which may be atherosclerotic or a hemodynamic phenomenon.

The major point to emphasize is that these patients should be followed very closely in the office or in the clinic and if any sign or symptom of deterioration is noted, prompt angiographic study should be carried out, hopefully before irrevocable changes have taken place with thrombosis. They can be corrected in the ways that Dr. Szilagyi outlined.

The first slide shows a 2-year-old vein graft which was implanted in the right femoro-popliteal area of a man in whom the saphenous veins had previously been stripped. This graft is a cephalic vein graft and it functioned well for 2 years. Abruptly, impending gangrene of the great toe developed which was extremely painful. The pedal pulses were still present. An angiogram showed a 95% stenosis for one or two millimeters which was interpreted as being a fused valve. The patient was operated upon and a homologous vein graft bypass was implanted into the old graft and the intervening segment removed. The slide shows the fused valve with a tiny probelike opening. The graft has functioned well for another 2 years. The next slide shows another view of the specimen.

The next slide is of a patient who was operated upon 2 years earlier with a cephalic vein bypass. He had previously had his saphenous veins stripped. This graft functioned well until he suddenly developed pain and coldness of the foot over a 12-hour period. Examination showed that the graft had closed. Thromboendarterectomy of the vein graft was performed with successful outcome. The slide shows thickening of the intima of the vein graft and there is an organizing thrombus. Also, a fresh thrombus of an estimated 12-hour duration is to be noted. It is amazing how long this must have been going on without producing obvious clinical symptoms until the acute thrombosis developed.

The next slide shows a saphenous vein graft inserted 2½ months earlier from the common femoral artery to the distal popliteal. He did well for 2½ months when suddenly his great toe began to pain him. It was blue. Pulses were still present in the foot. An angiogram showed a marked stenosis of about 1 cm. near the distal end of the vein graft, proximal to the distal anastomosis. The specimen removed showed profound thickening which our pathologist tells us is intimal fibrosis. A fat stain showed no lipid deposit. The lumen was almost completely occluded.

Once again, I think Dr. Szilagyi has done us a great service in presenting a beautifully documented paper which shows us how much can be done if these patients are followed carefully and are treated promptly.

Dr. H. William Scott, Jr. (Nashville): I wish principally, to call the attention of this audience to some experimental observations made in our laboratory in recent years concerning the behavior of autogenous venous grafts in animals which are exposed to an atherogenic dietary regimen.

This first slide summarizes an experimental study of responses of venous grafts implanted in the systemic arterial circuit in dogs.

Eight dogs in this group had autogenous jugular vein grafts inserted by suture into the abdominal aorta. They were exposed to a high cholesterol diet for 7 to 12 months, average serum cholesterol was maintained at a range of 424 to 1336 mg/100 ml.

At sacrifice, atheroma of gross severity was present ranging from minimal to severe degree in each of the eight animals, but in five of the eight only minimal atheroma was found in the host aorta.

In contrast, in each of the venous grafts which remained patent (one was occluded), there was severe atheroma of diffuse degree consistently present.

In controls on ordinary regular diet, vein grafts and host aortas showed no disease.

From this and multiple additional experiments with the same results, we have concluded that in animals maintained on a atherogenic diet under the rigorous experimental conditions of this study, the autogenous venous graft implanted in the systemic arterial circuit has a greater avidity for atheroma than does the host artery.

This slide shows examples of the severity of gross atheroma in the aorta and in the vein grafts. These are gross specimens fixed in formalin and stained with Sudan-IV to show the lipid deposits in the subintimal tissues.

Another group of experimental studies of vein grafts in the aorta is illustrated here.

In this study control animals with vein grafts in the aorta were maintained on an atherogenic diet for a period of up to 12 months, and similar grafts were done in a test group kept on diet for the same period, which have been protected by preliminary use of distal intestinal bypass.

None of the animals in the group with ilial by-pass, all of which had vein grafts in the distal aorta, showed any evidence of atheroma in the vein graft or in host aorta.

In the control group, an example of which is shown here, the vein grafts showed consistently severe atheroma.

The autogenous vein graft is an extremely valuable arterial substitute in clinical vascular surgery. When it is used in treatment of atherosclerotic segmental disease, however, we should be keenly aware that the fundamental metabolic atherogenic status of the patient persists.

Dr. Ralph A. Deterling, Jr. (Boston): Dr. Szilagyi has provided us with another one of his scholarly analyses of long-term results.

It is of some interest that there has been a long-time awareness of difficulty with vein grafts since historically one of the earliest grafts done by Lexar, I believe, around 1916 namely developed an aneurysm.

Having been associated with interest in synthetic grafts, we moved, with virtually the entire field, to the use of vein grafts and are sharing now some of the complications that Dr. Szilagyi has shown so nicely.

We have also been interested in the assessment of the total patient who has difficulty with peripheral vessels. I would like to ask Dr. Szilagyi if in his analysis of these patients who demonstrated either symptomatic or angiographic evidence of significant disease, did he find other evidence of new significant atherosclerotic vascular disease to a greater extent in those patients compared to his whole group?

Secondly, what must be done in a patient who has run out of saphenous veins? Dr. Szilagyi showed some patients in whom he was still able to use the opposite ones.

We described a compound graft about 15 years ago which we have had little occasion to use. It had a synthetic central portion and small pieces of vein with anastomosis and flexion pieces. I am curious as to whether he has had any occasion to use that graft or what other approach he would consider for these patients who continue to have complications.

Dr. Paul Nemir, Jr. (Philadelphia): In reviewing the results of bypass grafts at our institution, we too have been impressed with the importance of the atherogenic tendencies of the host on the long-term fate of the graft. This has manifested itself in different ways between the arterial homograft on the one hand and the vein graft on the other hand, though this may be more apparent than real in view of a difference in the site of the implant.

In patients with severe generalized atherosclerosis in whom we had the opportunity to study the aortic or iliac homografts, the atherosclerotic process developed in a rather uniform manner throughout the graft.

With the vein graft, however, the major problem has seemed to be, at least in our experience, at the inflow or at the outflow and there has been minimal involvement of the body of the graft.

This 54-year-old woman illustrates the problem in this group of patients with severe atherosclerosis. She was first seen with severe ischemia of the left leg resulting from a block of the superficial femoral artery. A femoro-popliteal vein graft was performed 6 years ago.

She came back about 2 years later with the same symptoms and a marked delay in the filling of the vein graft with a partial obstruction at the inflow tract. This was corrected by passing a graft from the iliac artery down to the previously implanted vein graft. She returned 9 months later with right leg ischemia and an arteriogram showed a complete block of the right superficial femoral artery, and a narrowing at the previous left femoro-popliteal anastomosis. The right side was corrected with a bovine heterograft femoro-popliteal bypass.

A subsequent arterial study showed continued narrowing at the left femoro-popliteal anastomosis, necessitating passing another graft from the original vein graft down to the posterior tibial artery. We certainly would agree on the importance of careful follow-up. I would like to ask Dr. Szilagyi if he uses any measures routinely to attempt to alter an atherogenic tendency and if in his excellent follow-up studies there has been any influence on the fate of the implants where he has tried to do this.

Dr. D. Emerick Szilagyi (Closing): I am grateful to the discussors for touching on some aspects of my topic that I had no time to deal with.

It is gratifying that Dr. Lord's experience agrees with ours.

Dr. Scott's work on experimental atherogenesis is well-known and important. Although observations have been reported that are different from his, I find his findings most convincing and certainly in accord with clinical experience.

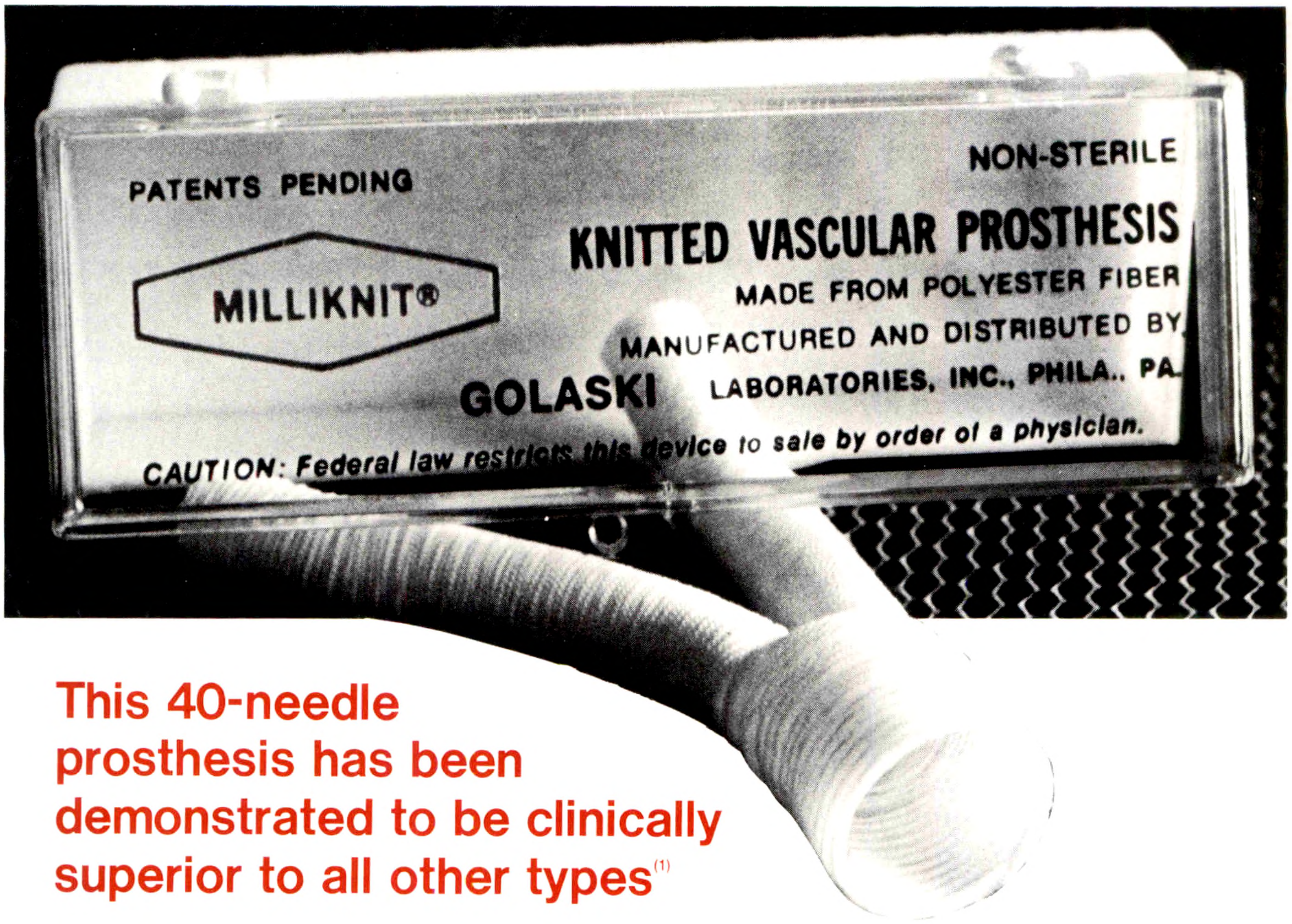
As regards Dr. Deterling's question, I should like to point out that there are four potentially useful veins to make recourse to, but assuming that there is no available venous transplant material, I would not hesitate to use a good quality Dacron graft, provided the operation was urgent, that is, if without it the patient would lose his leg or be incapacitated to support himself.

Both Dr. Deterling and Dr. Nemir touched on the question of a possible increased tendency to atherosclerosis in the patients with atherosclerotic changes in the vein grafts. We have rather extensive data on the known atherogenic factors in all our patients, both in those with and in those without atherosclerotic changes in the grafts, and we find no significant difference in this respect between those with and those without graft alterations. Atherosclerotic patients as a group, of course, have a somewhat higher incidence of blood lipid abnormalities than a comparable non-atherosclerotic patient population. Nor was the systemic atherosclerotic process more extensive or more advanced in those with changes in the grafts than in those without changes.

The question raised by Dr. Nemir whether one should use some prophylactic measures to delay or prevent the atherosclerotic graft changes is of great practical importance. As our knowledge now stands, the only proven atherogenic factor that one can control with a reasonable expectation of success is the use of tobacco. We do strenuously warn our patients about the need to stop smoking. A low-fat diet with emphasis on the use of polyunsaturated fats is also a reasonable measure; we recommend it but I doubt that we can effectively enforce it.

There are two practical points that I should like to take a minute to mention. The question naturally arises whether these observations are applicable to the venous autografts used in aorto-coronary bypasses. I believe they do. Moreover, all the known factors that hasten degenerative changes in the vein grafts such as intraluminal arterial pressure, narrowed outflow tracts causing unfavorable distal hemodynamics, tissue environment, and asymmetry between the dimensions of the graft and those of the recipient artery are unfortunately augmented in aorto-coronary operations. Secondly, it would be well to bear in mind that basic physiologic considerations suggest that the shorter the warm ischemia time of the venous graft the less tissue damage one can expect. We have laboratory studies yet unpublished that strongly suggests that this is indeed the case. All efforts should be made, therefore, not to remove the vein from its bed until all its tributaries have been carefully tied, and the moment the vein is mobilized it should be cooled in a glucose solution of about 2–3° C.

As a final remark, I would like to mention the intriguing relevance of these observations to the very broad and profound question of the etiology of atherosclerosis. When one realizes that a vein never shows evidences of atherosclerosis when it is in its normal anatomical and physiological environment but as soon as it is transposed in the hemodynamic environment of the arterial system it readily develops atherosclerosis, one cannot fail to conclude that hemodynamic factors are of cardinal importance in the etiology of atherosclerosis.


PATENTS PENDING
NON-STERILE
MILLIKNIT®
KNITTED VASCULAR PROSTHESIS
MADE FROM POLYESTER FIBER
MANUFACTURED AND DISTRIBUTED BY
GOLASKI LABORATORIES, INC., PHILA., PA.
CAUTION: Federal law restricts this device to sale by order of a physician.

This 40-needle prosthesis has been demonstrated to be clinically superior to all other types(1)

- In clinical use since 1962
- Long term patency with excellent residual flexibility(1)
- Preclots efficiently in heparinized blood(5)
- Lowest calcification index(1)

Ten solid years of engineering and physiological studies are behind this product. The original graft was developed and produced by W. M. Golaski in collaboration with Dr. S. A. Wesolowski. Its superior handling and healing properties are attributable to the exclusive Golaski designed 40-needle-to-the-inch knit.

Available in MILLIKNIT® and MICROKNIT® construction for a wide range of applications. MILLIKNIT (40-needle) is offered in a complete range of bifurcations, tubes, and patches. MICROKNIT (50-needle), which has even more efficient preclotting ability, is offered in straight tube sizes and patches.

Both MILLIKNIT and MICROKNIT are available internationally. Write for further information.

Visit us at ACS Clinical Congress, Chicago, Oct. 14-18

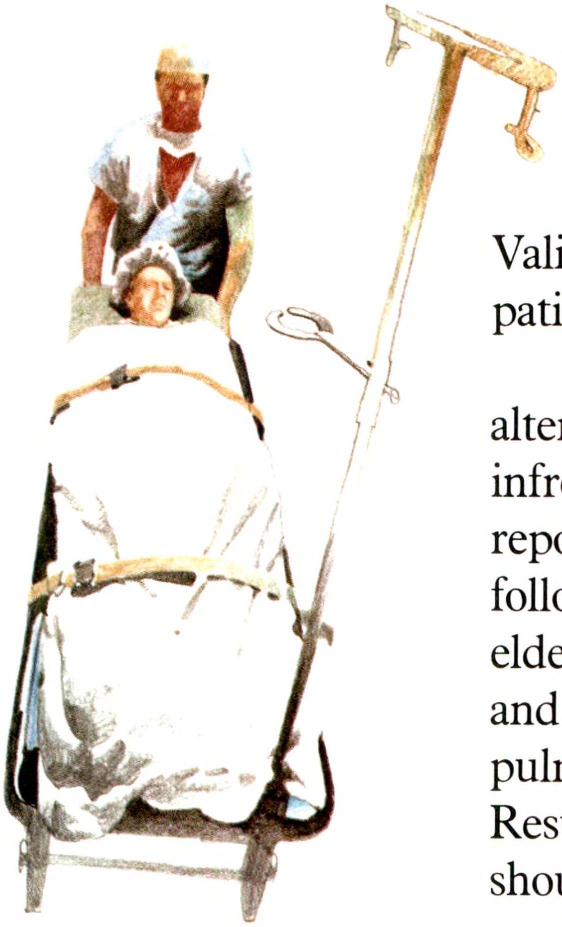
GOLASKI LABORATORIES, INC.
4567 Wayne Avenue, Philadelphia, Pa. 19144 Telephone: 215-222-3339; 215-843-4567

Partial list of references: (1) Wesolowski, S.A., PERFORMANCE OF MATERIALS AS PROSTHETIC BLOOD VESSELS, printed in the BULLETIN OF THE N.Y. ACADEMY OF MEDICINE (Feb., 1972). (2) Golaski, W.M., ENGINEERING DESIGN FACTORS IN THE CONSTRUCTION AND EVALUATION OF KNITTED ARTERIAL PROSTHESES. Paper presented at Materials Conference, A.I.C.E. (1968). (3) Wesolowski, S.A., EVALUATION OF TISSUE AND PROSTHETIC VASCULAR GRAFTS (1962). (4) Wesolowski, S.A., Dennis, C., FUNDAMENTALS OF VASCULAR GRAFTING (1963). (5) Wesolowski, S.A., Fries, C.C., McMahon, J.D., Martinez, A., EVALUATION OF A NEW VASCULAR PROSTHESIS WITH OPTIMAL SPECIFICATIONS (1966)

Facing surgery with acute anxiety

You expect your preoperative patient to be somewhat anxious and apprehensive about the scheduled surgery. But in some cases, psychic tension reaches undesirable levels as the time for the procedure approaches.

In such situations, 10 mg Injectable Valium® (diazepam), administered I.M. an hour or two before the operation, can lessen the undue anxiety and tension associated with strange surroundings and disturbing procedures. The calming effect is generally prompt and pronounced. What's more,



Valium (diazepam) can markedly reduce the patient's recall of preoperative procedures.

Injectable Valium seldom significantly alters vital signs. Nevertheless, there have been infrequent reports of hypotension and rare reports of apnea and cardiac arrest, usually following I.V. administration, especially in elderly or very ill patients and those with limited pulmonary reserve. Resuscitative facilities should be available.

When given in conjunction with narcotics, a reduction of narcotic dosage should be considered. (See prescribing information.)

Do not mix or dilute Injectable Valium with other drugs, solutions or fluids. The 10-mg disposable syringe is especially useful in this respect, since it provides a convenient method of using Valium and at the same time helps assure aseptic handling.

Injectable Valium® (diazepam) can ease the way

ROCHE

Before prescribing, please consult complete product information, a summary of which appears on the following page.

Prior to surgery, to relieve excessive anxiety; additionally, may diminish recall

Injectable Valium® (diazepam)

ready-to-use 2-ml Tel-E-Ject® (disposable syringes)
10-ml vials
2-ml ampuls
5 mg/ml

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states, somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus and severe recurrent seizures; anxiety prior to gastroscopy, esophagoscopy, and surgical procedures; cardioversion (I.V.).

Contraindicated: In infants; in patients with known hypersensitivity to the drug; in acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *Inject I.V. slowly, directly into vein; take at least one minute for each 5 mg (1 ml) given. Do not mix or dilute with other solutions or drugs. Do not add to I.V. fluids.* Rare reports of apnea or cardiac arrest noted, usually following I.V. administration, especially in elderly or very ill and those with limited pulmonary reserve; duration is brief; resuscitative facilities should be available. Not recommended as sole treatment for psychotic or severely depressed patients. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. Caution against hazardous occupations requiring complete mental alertness. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lacation or women of childbearing age, weigh potential benefit against possible hazard to mother and child.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Not recommended for bronchoscopy, laryngoscopy, obstetrical use, or in diagnostic procedures other than gastroscopy and esophagoscopy. Laryngospasm and increased cough reflex are possible during gastroscopy; necessary countermeasures should be available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Since effect with narcotics may be additive, appropriate reduction in narcotic dosage is possible. Use lower doses (2 to 5 mg) for elderly and debilitated. Safety and efficacy in children under 12 not established.

Side Effects: Drowsiness, fatigue, ataxia, confusion, depression, constipation, dysarthria, diplopia, headache, hypoactivity, hiccups, hypotension, incontinence, jaundice, nausea, changes in libido, changes in salivation, phlebitis at injection site, urinary retention, skin rash, syncope, slurred speech, urticaria, tremor, vertigo, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial adult dose is 2 to 10 mg I.M. or I.V., depending on indication for use. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Precautions and Adverse Reactions.) In gastroscopy and esophagoscopy, 5 to 10 mg, I.M. or I.V., 30 min. prior to procedure. As preoperative medication, 10 mg, I.M., 1 to 2 hours before surgery. In cardioversion, 5 to 15 mg, I.V., within 5 to 10 min. prior to procedure. Give I.V. injections slowly; take at least 1 minute for each 5 mg (1 ml).

In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory; not more than 30 mg should be given within 8-hour period. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Supplied: Valium® (diazepam) Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

...because patients
respect your judgment,
trust your experience

Darvon®
Compound-65

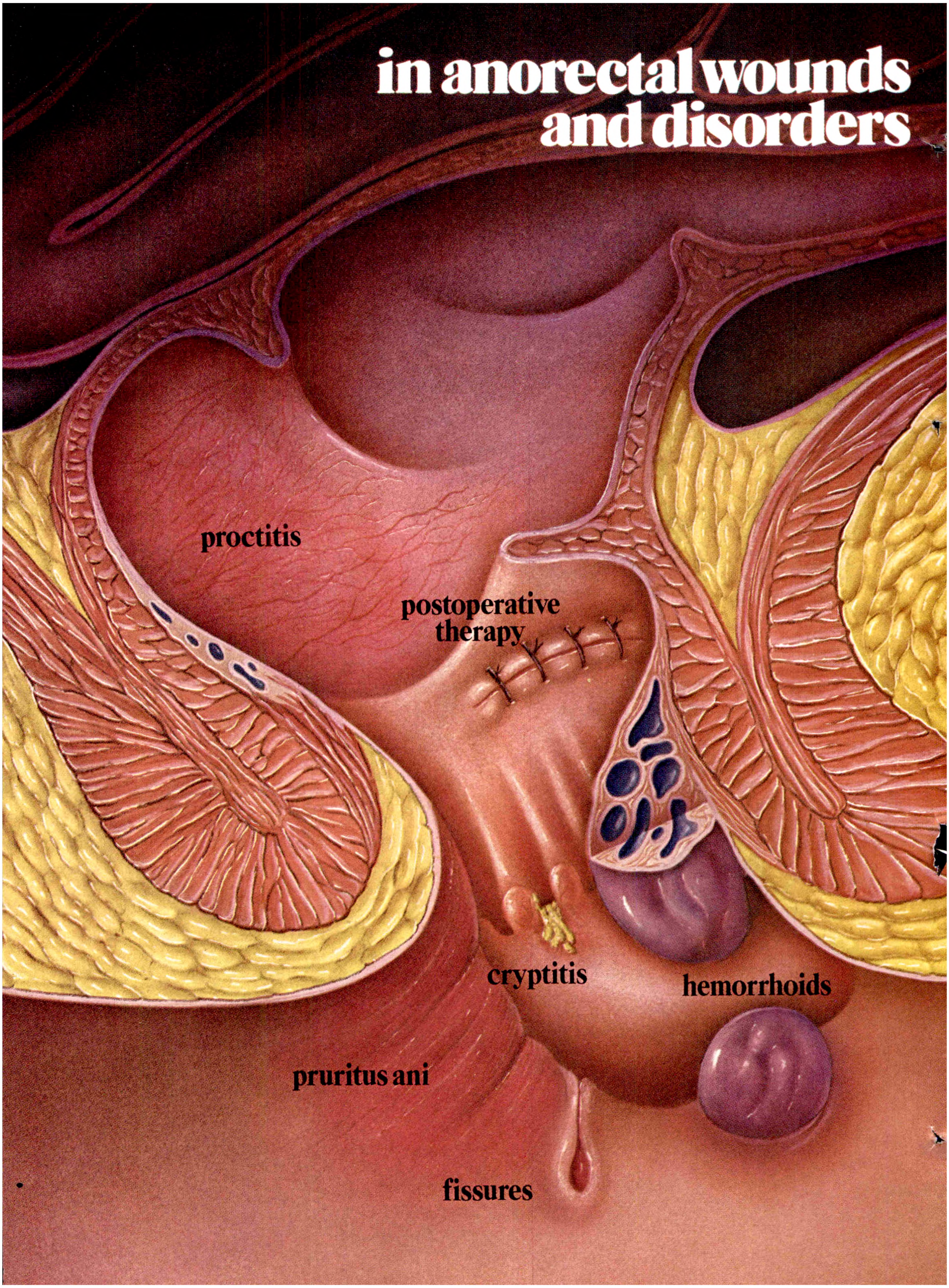
65 mg. propoxyphene hydrochloride, 227 mg. aspirin,
162 mg. phenacetin, and 32.4 mg. caffeine

made in the Lilly tradition

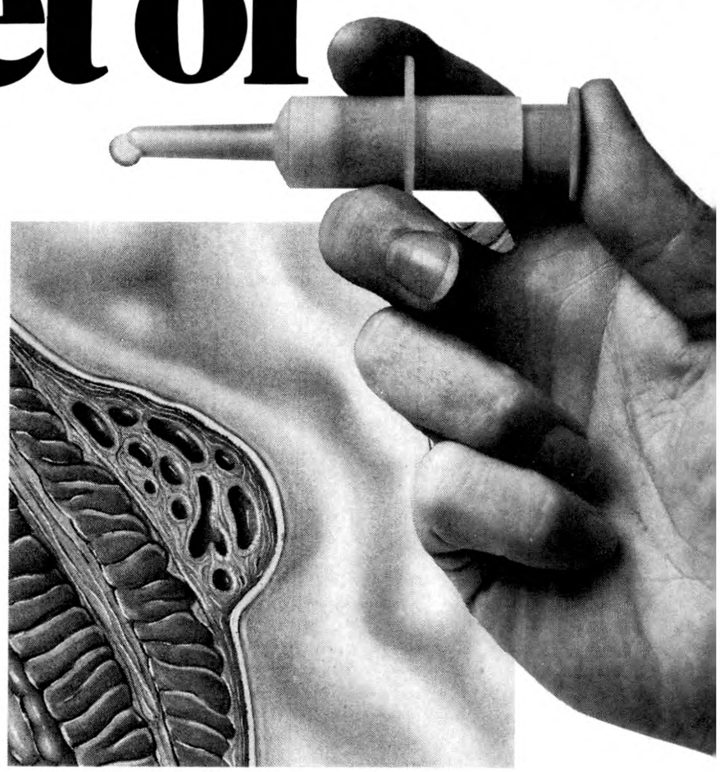
Lilly

301024

Eli Lilly and Company
Indianapolis, Indiana 46206


in anorectal wounds and disorders
proctitis
postoperative therapy
cryptitis
hemorrhoids
pruritus ani
fissures

...Blanket of Relief



Proctofoam®-HC, unique mucoadhesive foam, medicates the anorectal mucosa more rapidly and thoroughly than suppositories[1-6]

- better contact with the involved tissues;[1-6] spreads evenly throughout anal canal, rectal crypts, papillae and hemorrhoidal sites.
- unlike suppositories, won't "bypass" areas of pathology often missed by creams and suppositories.[1,4,5,6]
- unlike suppositories[5]—spreads evenly, with no need to melt.

Proctofoam-HC offers greater promise of a short and pain-free postoperative period

- faster wound healing[1-3,5] (2½ to 3 weeks instead of the expected 3½ to 4 weeks).[5]
- less scar formation—wounds more pliable, with clean, healthy-looking, granulating tissue.[1-3]
- less edema, inflammation, swelling, itching, pain and tenesmus.[1,3,5,6]
- preferred by patients over other forms of therapy.[1,4,5]

Compared to suppositories, Proctofoam-HC provides greater patient comfort, convenience and economy

- measured-dose applicator facilitates self-administration with minimal discomfort[1] and eliminates finger contact with perianal area.
- mucoadhesive foam won't leak or stain.[2,4]
- foam container requires no refrigeration.
- less than half the cost of hydrocortisone-containing suppositories per application.

unique mucoadhesive foam

Proctofoam®-HC

Each measured dose (approx. 6.5 ml.) delivers hydrocortisone acetate 1%, pramoxine hydrochloride 1%, in a water-soluble, mucoadhesive foam base.

antiinflammatory/antipruritic/analgesic

References: **1.** Bernstein, I.: *Surg. Dig. 4*:23, Jan. 1969. **2.** Sladek, W. R.: Scientific Exhibit, 69th Annual Meeting of American Proctologic Society, April 1970. **3.** Sladek, W. R.: *Amer. J. Clin. Res. 1*:33, Jan.-Feb. 1970. **4.** O'Brien, J. R.: *Surg. Dig. 4*:27, April 1969. **5.** Miller, H.: *Amer. J. Proctol. 18*:59, Feb. 1967. **6.** Lieberman, W.: *Amer. J. Proctol. 20*:134, April 1969.

Active Ingredients: Hydrocortisone acetate, 1%, and pramoxine hydrochloride, 1%, in a mucoadhesive foam base.

Indications: Temporary relief of anorectal inflammation, pruritus, pain and swelling associated with hemorrhoids, proctitis, cryptitis, fissures, postoperative pain and pruritus ani.

Contraindications: Abscess, extensive fistulas or sinus tracts, tuberculosis, varicella, vaccinia or acute herpes simplex.

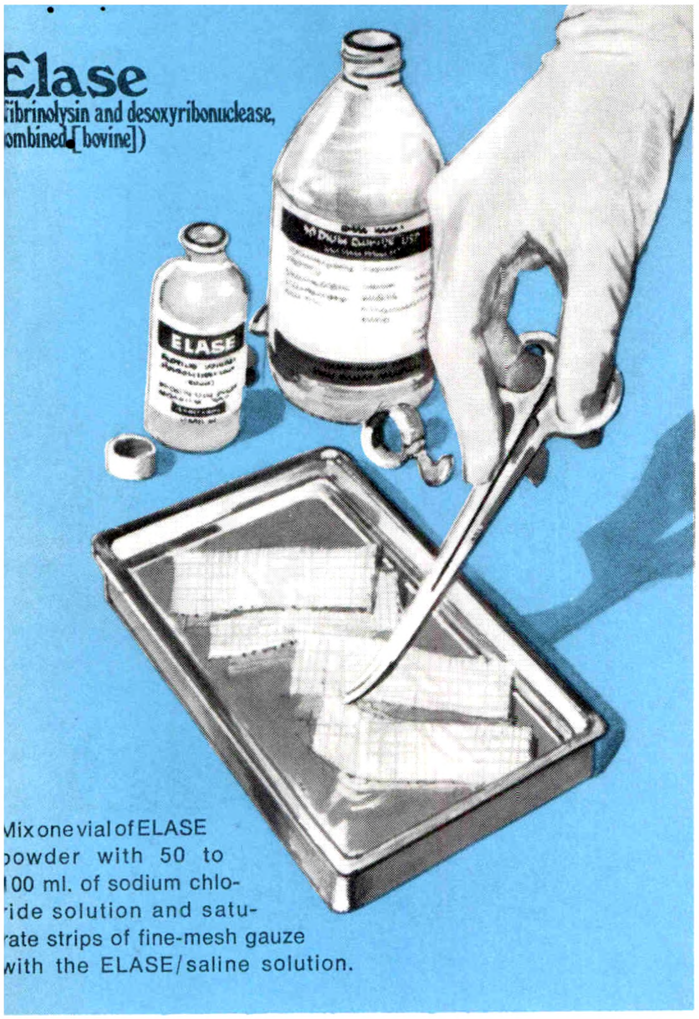
Precautions: A complete rectal examination to rule out serious pathology should be completed before instituting therapy. Do not use on infected lesions unless accompanied by antiinfective agents. Discontinue use if sensitivity develops.

Caution: Do not insert any part of the aerosol container into the anus. Contents of the container are under pressure, but not flammable.

Dosage: One applicatorful two or three times daily and after each bowel evacuation. Perianally, apply as needed.

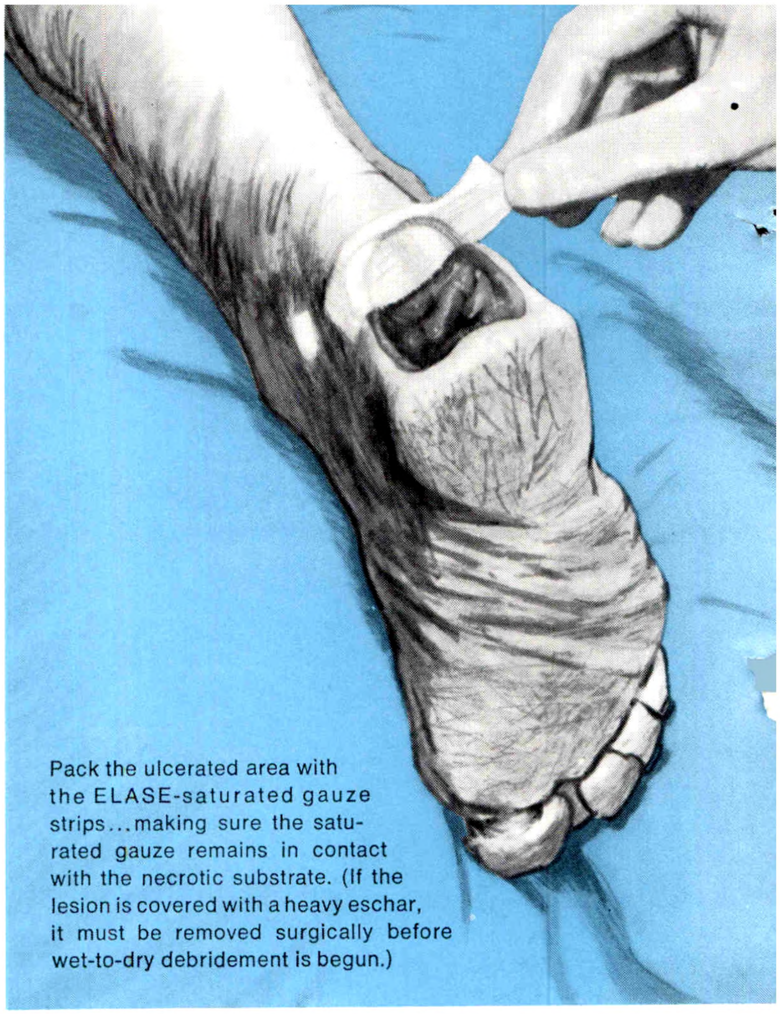
How Supplied: In aerosol container providing 15 Gms. of medication (approx. 25 applications) with special rectal applicator and patient instructions.

Reed & Carnrick/Kenilworth, N.J. 07033

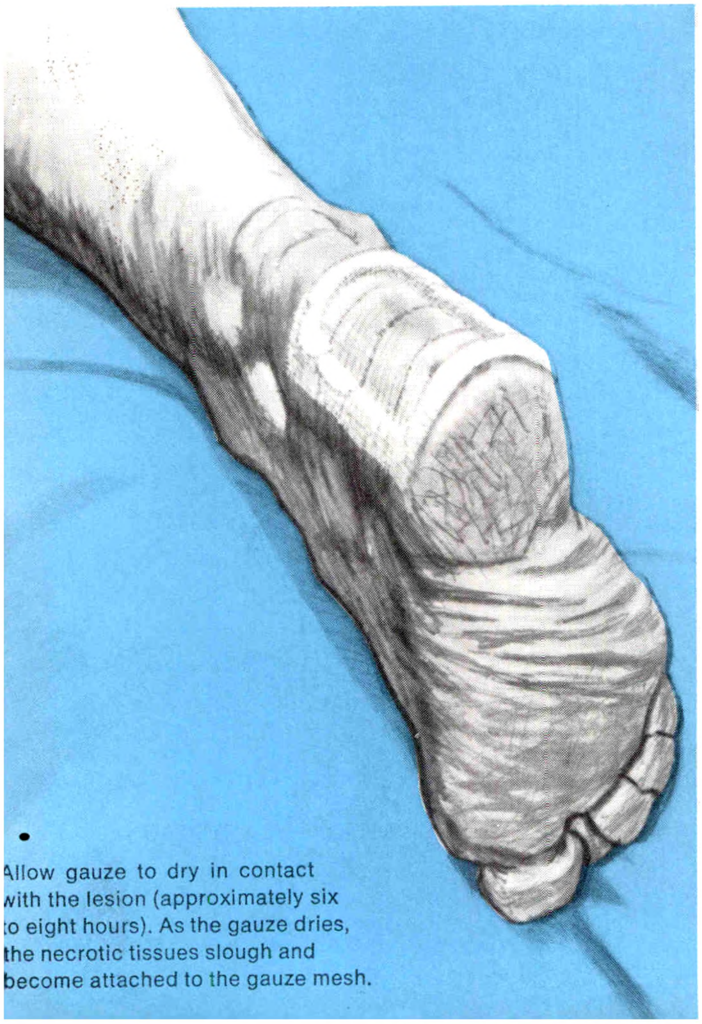


Elase
fibrinolysin and desoxyribonuclease, combined [bovine])

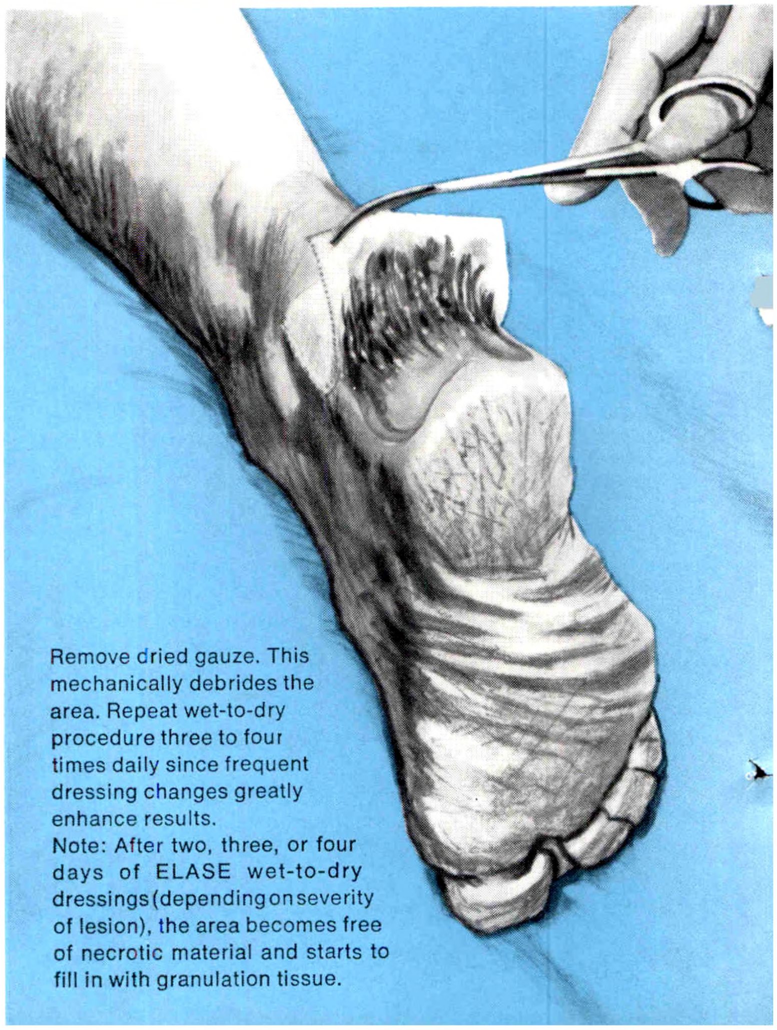
Mix one vial of ELASE powder with 50 to 100 ml. of sodium chloride solution and saturate strips of fine-mesh gauze with the ELASE/saline solution.



Pack the ulcerated area with the ELASE-saturated gauze strips...making sure the saturated gauze remains in contact with the necrotic substrate. (If the lesion is covered with a heavy eschar, it must be removed surgically before wet-to-dry debridement is begun.)



Allow gauze to dry in contact with the lesion (approximately six to eight hours). As the gauze dries, the necrotic tissues slough and become attached to the gauze mesh.



Remove dried gauze. This mechanically debrides the area. Repeat wet-to-dry procedure three to four times daily since frequent dressing changes greatly enhance results.

Note: After two, three, or four days of ELASE wet-to-dry dressings (depending on severity of lesion), the area becomes free of necrotic material and starts to fill in with granulation tissue.

the new way is wet-to-dry ...debridement with

Elase® solution

(fibrinolysin and desoxyribonuclease, combined [bovine])

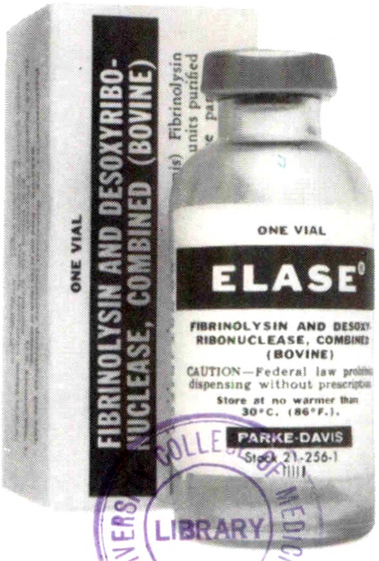
INDICATIONS: Elase is indicated for topical debridement in general surgical wounds, ulcerative lesions, burns, circumcision and episiotomy, and in cervicitis and vaginitis. Elase is used as an irrigating agent in infected wounds, otorhinolaryngologic wounds, and superficial hematomas (except when the hematoma is adjacent to or within adipose tissue).

CONTRAINDICATIONS: Elase is contraindicated in individuals with a history of hypersensitivity reactions to any of the components. Elase is not recommended for parenteral use since the bovine fibrinolysin may be antigenic.

PRECAUTIONS: The usual precautions against allergic reactions should be observed, particularly in persons with a history of sensitivity to materials of bovine origin or to mercury compounds.
To be maximally effective, Elase solutions must be freshly prepared before use. The loss in activity is reduced by refrigeration; however, even when stored in a refrigerator, the solution should not be used 24 hours or more after reconstitution.

ADVERSE REACTIONS: Side effects attributable to the enzymes have not been a problem at the dose and for the indications recommended. With higher concentrations, local hyperemia may be a side effect.

HOW SUPPLIED: Elase (powder) is supplied dried in 30-cc. rubber-diaphragm-capped vials containing 25 units (Loomis) of fibrinolysin and 15,000 units (modified Christensen method) of desoxyribonuclease with 0.1 mg. thimerosal (mercury derivative).
Elase Ointment is supplied in 30-Gm. tubes containing 30 units (Loomis) of fibrinolysin and 20,000 units of desoxyribonuclease with 0.12 mg. thimerosal and in 10-Gm. tubes containing 10 units of fibrinolysin and 6,666 units of desoxyribonuclease with 0.04 mg. thimerosal.

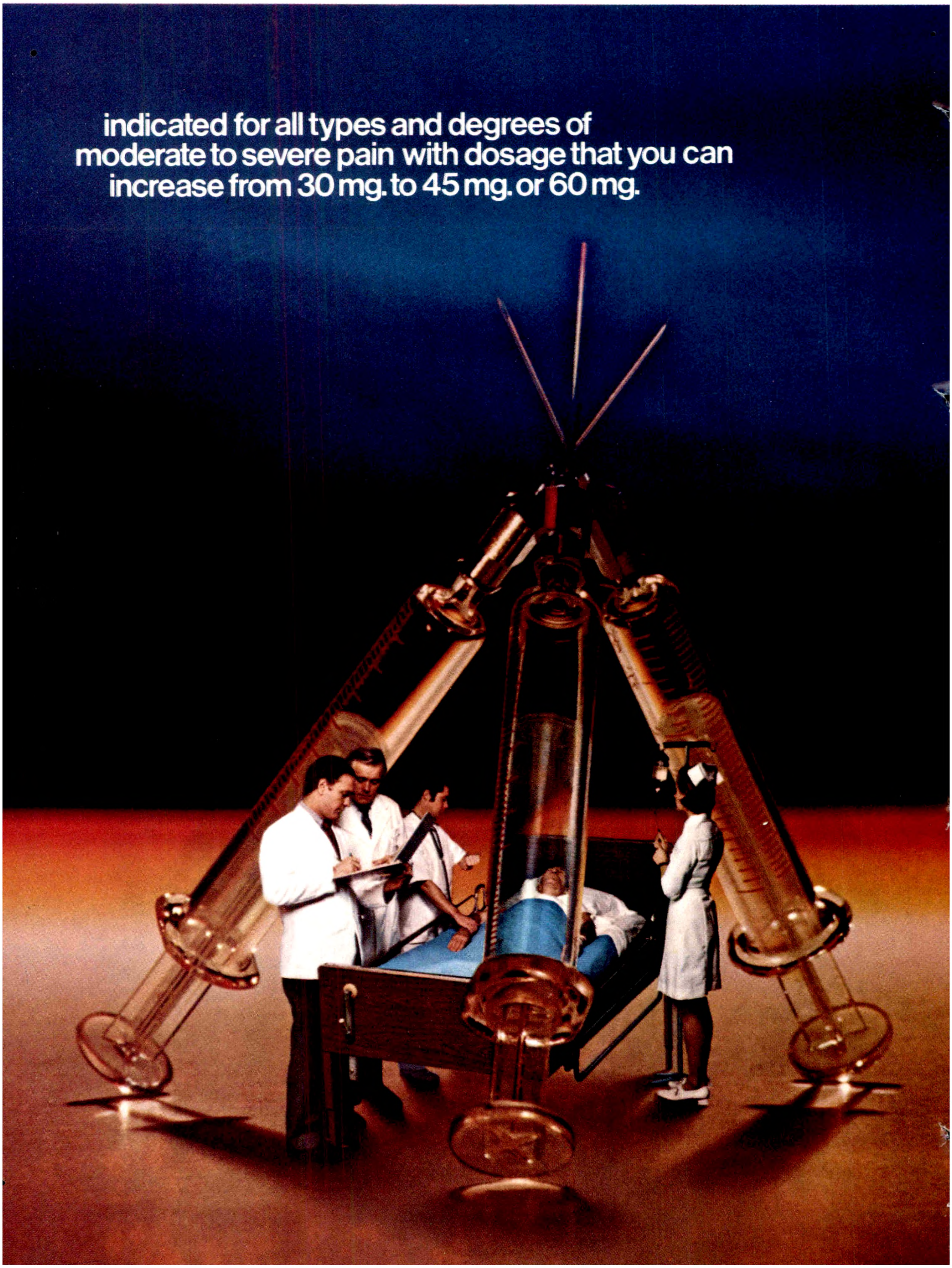

ONE VIAL
FIBRINOLYSIN AND DESOXYRIBO-NUCLEASE, COMBINED (BOVINE)
ONE VIAL
ELASE®
FIBRINOLYSIN AND DESOXY-RIBONUCLEASE, COMBINED (BOVINE)
CAUTION—Federal law prohibits dispensing without prescription
Store at no warmer than 30°C. (86°F.).
PARKE-DAVIS
Stock 21-256-1

UNIVERSITY COLLEGE OF MEDICINE LIBRARY

PARKE-DAVIS

Parke, Davis & Company, Detroit, Michigan 48232

HF PA 593 102171


indicated for all types and degrees of
moderate to severe pain with dosage that you can
increase from 30 mg. to 45 mg. or 60 mg.

An analgesic as potent as you need

Type of pain	Dosage	No. patients studied	Incidence of excellent to good analgesia	Adverse Reactions
post-operative pain[1]*	**30 mg.**	29	79.3%	"As the study progressed, the dosage was increased to 45 and 60 mg. to determine whether higher doses would produce greater analgesia without an increase in adverse effects."[1] "Only a few minor side effects were observed."[1]
	45 mg.	70	83.0%	
	60 mg.	101	94.0%	
post-operative pain[2]†	**30 mg. or 60 mg.**	68	94.0%	"At the start of the study, adult patients were given 30 mg. doses. It was found, however, that a 60 mg. dose gave better analgesia with no noticeable difference in tolerance."[2]

*Study based on response to a single dose.

†Study based on multiple doses, according to patient need.

References: 1. Finestone, S. C. and Katz, J.: Pentazocine as a postoperative analgesic, *Anesth. Analg.* 45:312, May-June 1966. 2. Snow, E. W.: Pentazocine—clinical evaluation, *Abdom. Surg.* 9:150, May 1967.

Provides relief comparable to that of morphine and meperidine, but with fewer significant adverse effects††

- Compared to morphine, Talwin causes less severe respiratory depression, hypotension, urinary retention, constipation.
- Compared to meperidine, Talwin is less likely to cause nausea, vomiting, diaphoresis.
- Not subject to narcotic controls.

††See next page for a complete discussion of Warnings, Precautions, Adverse Reactions, and other Prescribing Information.

Injectable

Talwin® brand of **pentazocine** (as lactate)

30 mg. 45 mg. 60 mg.

Talwin®
Brand of **pentazocine** (as lactate)
Analgesic for Parenteral Use

Ampuls: 30 mg. (1 ml.), 45 mg. (1½ ml.), and 60 mg. (2 ml.)
Vials: (10 ml.) 30 mg./ml.
30 mg. for I.V., I.M., or S.C. use
45 mg. for I.M. or S.C. use
60 mg. for I.M. or S.C. use

Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.*

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced mild withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *other:* tachycardia, soft tissue induration, nodules, cutaneous depression, and ulceration (sloughing) at the injection site, weakness or faintness, chills, moderate transient eosinophilia, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

How Supplied: *Ampuls of 1 ml. (30 mg.), 1½ ml. (45 mg.), and 2 ml. (60 mg.)* in boxes of 25. Each 1 ml. contains Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

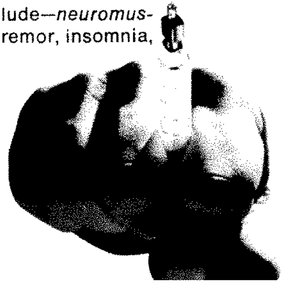
Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide. The air in the ampuls and vials has been displaced by nitrogen gas.

Winthrop Laboratories, New York, N.Y. 10016

Winthrop

bulwark against pain
of moderate to severe intensity

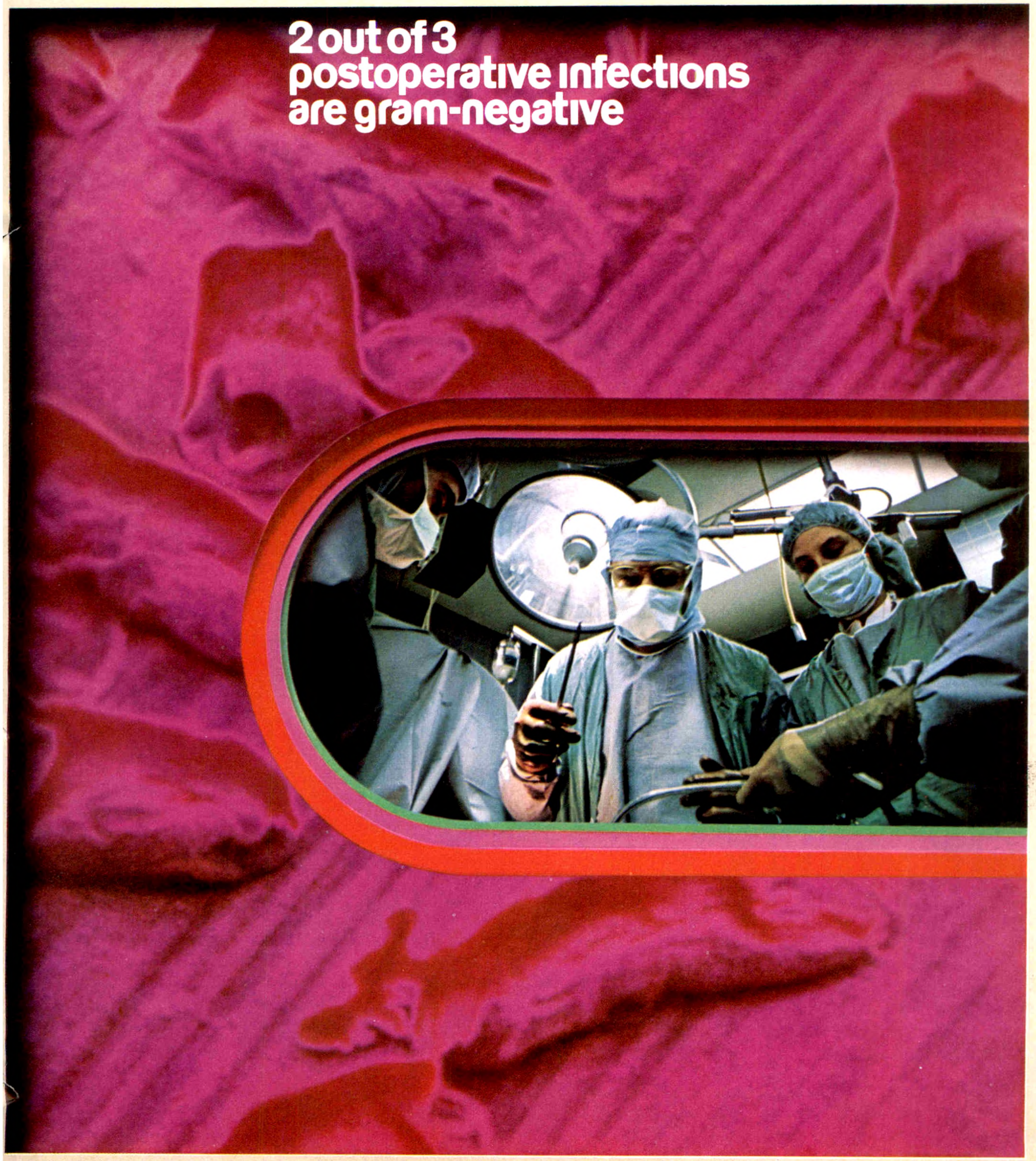


Injectable
Talwin®
brand of
pentazocine
(as lactate)

(1617)

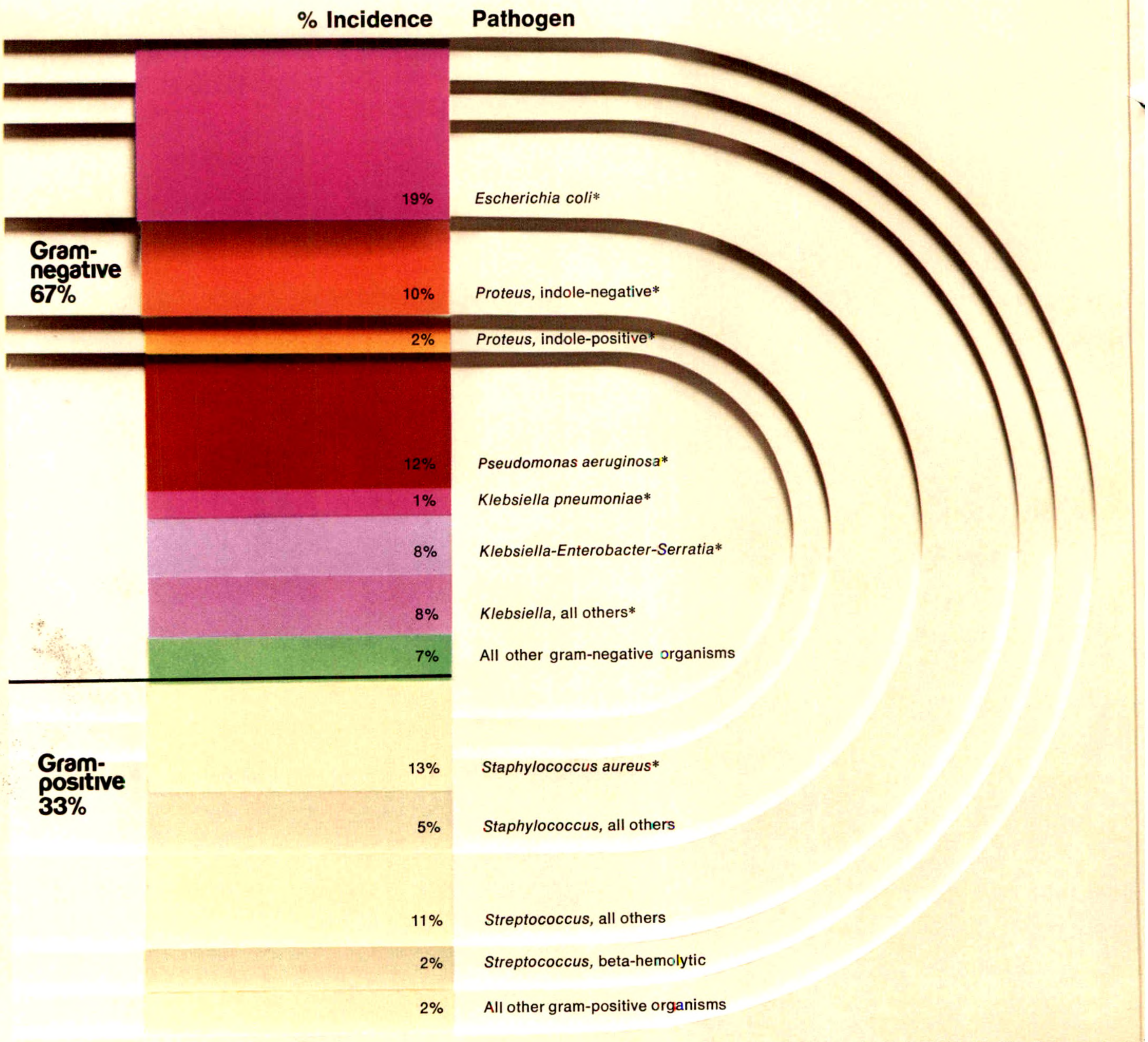
Schering

On the surgical service... a major problem



Gram-negative bacteria magnified 10,000 times—color-tinted

Commonly encountered pathogens on the surgical service



	% Incidence	Pathogen
Gram-negative 67%	19%	*Escherichia coli**
	10%	*Proteus*, indole-negative*
	2%	*Proteus*, indole-positive*
	12%	*Pseudomonas aeruginosa**
	1%	*Klebsiella pneumoniae**
	8%	*Klebsiella-Enterobacter-Serratia**
	8%	*Klebsiella*, all others*
	7%	All other gram-negative organisms
Gram-positive 33%	13%	*Staphylococcus aureus**
	5%	*Staphylococcus*, all others
	11%	*Streptococcus*, all others
	2%	*Streptococcus*, beta-hemolytic
	2%	All other gram-positive organisms

Total pathogens 3,492
Source: Gosselin Audit of Pathology Cultures—1971

*GARAMYCIN Injectable is effective against susceptible strains of the pathogens indicated.

Copyright © 1973, Schering Corporation. All Rights Reserved.

Schering

A highly appropriate spectrum for today's problem pathogens

GARAMYCIN Injectable offers a high probability of effectiveness against susceptible strains of seven out of seven major gram-negative pathogens. These are:

Escherichia coli
Proteus, indole-negative
Proteus, indole-positive
Pseudomonas aeruginosa
Klebsiella
Enterobacter } species
Serratia

GARAMYCIN Injectable has also been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

Start with Garamycin

■ **Broad gram-negative spectrum**
Because of its broad gram-negative spectrum and its well-established clinical efficacy, GARAMYCIN Injectable can be considered for initial therapy in suspected as well as documented gram-negative sepsis.

Stay with Garamycin

■ **Susceptibility of causative organisms confirmed**
The results of susceptibility tests will, in most cases, demonstrate the causative organisms' sensitivity to GARAMYCIN Injectable. However, the decision to continue therapy with this drug should also be based on the severity of the infection and the important additional concepts contained in the Warning Box.

■ **Relatively low incidence of adverse reactions**
Risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

■ **Bacterial resistance has not been a problem**
In the laboratory, resistance has been demonstrated to develop slowly in stepwise fashion. No one-step mutations to high resistance have been reported to date.

On the surgical service...

Garamycin®
gentamicin sulfate
injectable
I.M./I.V.

40 mg. per cc.
Each cc. contains gentamicin sulfate equivalent to 40 mg. gentamicin

In gram-negative septicemia, peritonitis, postoperative pneumonia, and urinary tract infections*

*Due to susceptible organisms

WARNING
Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

See Clinical Considerations section which follows...

Schering

On the surgical service...

in gram-negative septicemia, peritonitis, postoperative pneumonia, and urinary tract infections*

Garamycin®

gentamicin sulfate injectable

I.M./I.V.

40 mg. per cc.
Each cc. contains
gentamicin sulfate equivalent
to 40 mg. gentamicin

Also available:
GARAMYCIN® Pediatric Injectable, 10 mg. per cc.

GARAMYCIN® Injectable, brand of gentamicin sulfate U.S.P., injection, 40 mg./cc.
Each cc. contains gentamicin sulfate equivalent to 40 mg. gentamicin
For Parenteral Administration

WARNING
Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, Proteus species (indole-positive and indole-negative), **Escherichia coli** and **Klebsiella-Enterobacter-Serratia** species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin type drug is usually indicated as concomitant antimicrobial therapy.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, thrombocytopenia, purpura; fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:

PATIENTS WITH NORMAL RENAL FUNCTION*

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lb.), the usual dosage is 80 mg. (2 cc.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dose is 60 mg. (1.5 cc.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

*In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration, in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 cc. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution, in both instances should normally not exceed 1 mg./cc. (0.1%). The solution is infused over a period of 1 to 2 hours.

The recommended dose for intravenous administration is identical to that recommended for intramuscular use.

GARAMYCIN Injectable should not be physically pre-mixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per cc., 2 cc. multiple-dose vials for parenteral administration.

Also available, GARAMYCIN Pediatric Injectable, 10 mg. per cc., 2 cc. multiple-dose vials for parenteral administration. APRIL, 1972

AHFS Category 8:12.28

For more complete prescribing details, consult Package Insert or Physicians' Desk Reference. Schering literature is also available from your Schering Representative or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

---

*Due to susceptible organisms

SLR-299

Fifteen-Year Clinical Experience with the Vena Cava Filter

MARION S. DeWEESE, M.D.,* RICHARD O. KRAFT, M.D.,** W. KIRT NICHOLS, M.D.,*** HERBERT H. SIX, M.D.,† NORMAN W. THOMPSON, M.D.†*

From the Departments of Surgery of the University of Missouri Medical Center-Columbia, University of Michigan Medical Center-Ann Arbor, St. Joseph's Mercy Hospital-Ann Arbor, Ann Arbor Veterans Administration Hospital, Ann Arbor, Michigan

AN EXPERIMENTAL method for the construction of an intraluminal filter within the inferior vena cava to intercept potentially fatal recurrent pulmonary emboli was reported by the senior author and Hunter in 1958.[8] Encouraged by the results of this laboratory investigation, a clinical study utilizing this method was initiated in 1957 and a favorable experience with 24 patients treated during the ensuing 5 years was reported in 1963.[9] Since that time, we have continued our clinical investigation of this method with only minor modifications in our indications for operation and in operative technic. This study summarizes our experience with the vena cava filter during the period October 1957-October 1972.

Our laboratory studies, which began in 1955, were stimulated by our dissatisfaction with the late sequelae which we had observed in patients following ligation of the vena cava, a procedure which had been introduced by Homans a decade earlier.[16] We were stimulated by the earlier work of Streuter and Paine[44] and Pualwan *et al.*[34] who had evaluated the possible benefit of temporary ligation of the vena cava with absorbable (catgut) ligature, and by that of Moretz *et al.*[26] who occluded the vena cava temporarily with a removable metal clip. Although we were not aware of their experimental work with the permanent teflon vena cava clip at the time we initiated our studies, Moretz, Rhode and Shepherd[27] published a combined report of their laboratory and clinical studies in 1959 and merit recognition for their pioneering investigation of partial interruption technics. Spencer *et al.*[41] introduced the concept of vena cava *plication* in 1960 and their clinical reports in 1962 and 1965[42,43] did much to gain approval of the partial interruption concept. Although the filter procedure as employed by us, and plication as practiced by Spencer, are frequently confused, they are basically different procedures and each needs to be evaluated on its own merits. Generically, both are partial interruption procedures. In the plication procedure, however, the lumen of the vena cava is divided into multiple smaller channels whereas in the filter procedure the integrity of the caval lumen is maintained and reliance is placed upon an intraluminal sieve.

During the past decade, a number of other methods for effecting partial interruption of the vena cava have been proposed. These include extraluminal serrated clips which have been investigated by Miles *et al.*,[20,21] Adams and J. DeWeese,[1,2] and Taber and Lam.[45] Barkett, Wright and Greenfield[4] developed an extraluminal prosthesis with tapering channels which permit laminar blood flow. Sensening[37,38] and Ravitch[35] studied compartmentation of the vena cava with a mechanical vascular stapler. Whitcomb[46] modified the filter technic by constructing a grid within the vena cava by placing two rows of sutures at right angles to one another. Leather *et al.*[19] published a favorable experience with the Moretz

---

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25-27, 1973.

Supported in part by CRC Grant RR 00287-07 (University of Missouri).

* W. Alton Jones Professor and Chairman, Department of Surgery, University of Missouri, Columbia, Missouri.

** Clinical Professor of Surgery, University of Michigan and Chief of Surgery, St. Joseph's Mercy Hospital, Ann Arbor, Michigan.

*** Chief Resident in General Surgery, University of Missouri, Columbia, Missouri.

† Chief Resident in Thoracic and Cardio-vascular Surgery, University of Missouri, Columbia, Missouri.

†* Professor of Surgery, University of Michigan, Ann Arbor, Michigan.

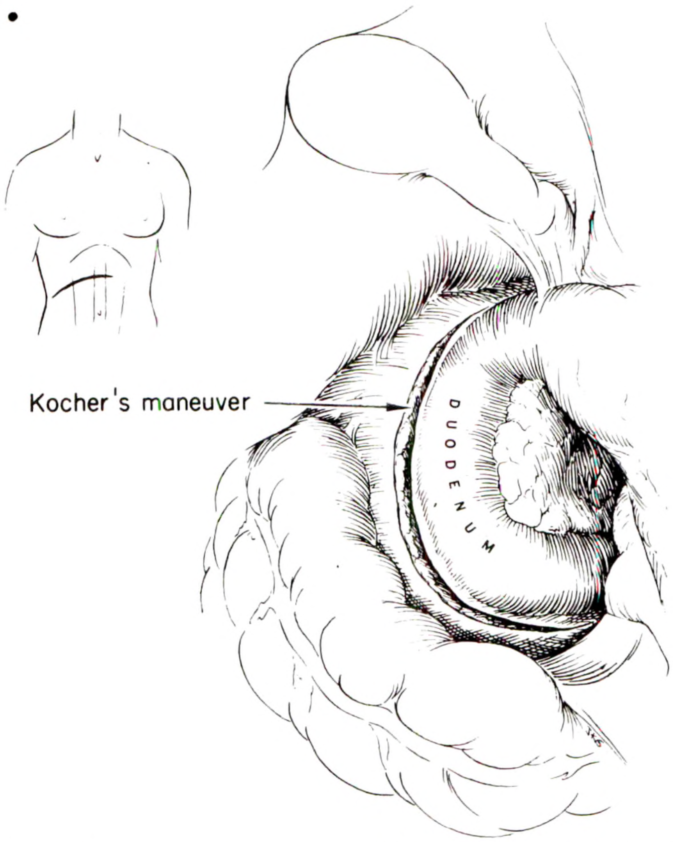


FIG. 1. Operative technic—upper abdominal transverse incision and mobilization of the duodenum.

clip in 1968 and summarized much of the cumulative data pertinent to the partial interruption procedures. Moretz *et al.*[28] summarized their long-term positive results recently, also.

Much work has been directed recently toward the development of methods by which filtering or occluding devices can be placed within the inferior vena cava by transvenous jugular or femoral routes. Mobin-Uddin *et al.*,[23] Eichelter and Schenk,[11] Pate *et al.*,[32] Hunter *et al.*,[17] Moser *et al.*[29] and Greenfield *et al.*[14] have developed devices and methods for partially or totally interrupting the vena cava transvenously and are subjecting them to clinical trial.

We will not attempt in this report to argue the merits of one form of caval interruption over another. Rather, we have persisted in our transperitoneal method of caval filtration over the past 15 years in an effort to accumulate data which would help us establish, or discredit, the *principle* of caval filtration, as opposed to total caval ligation, and it is this experience which we wish to report.

TABLE 1. *Distribution of Patients*

	Male	Female	Total
University of Missouri Hospital	10	24	34
University of Michigan Hospital	12	12	24
St. Joseph Mercy Hosp.—Ann Arbor	18	25	43
Veterans Administration Hospital—A²	11	0	11
	51	61	112

Materials and Methods

Study Sample

The patient population available for follow-up studies includes 112 patients who were operated upon during the period October 14, 1957 to October 14, 1972. The patients were treated in four different hospitals assuring representation of both sexes and of diverse socio-economic backgrounds (Table 1). Twelve of the patients included in our previous clinical report were not available to us for follow-up study, having been contributed by colleagues from other institutions.

Selection of Patients

Strict criteria for the selection of patients for operation were established at the outset of the study and have remained basically unchanged. These are:

1. Anticoagulant therapy (heparin and/or coumadin) constitutes the primary treatment of choice for patients with active thrombophlebitis and/or an initial pulmonary embolus.
2. A vena cava filter is advised *primarily* when:
   a) Recurrent pulmonary embolization occurs while the patient is at therapeutic levels of anticoagulation,
   b) The patient is intolerant of, or hypersensitive to, anticoagulant drugs,
   c) Hemorrhage, or threat of hemorrhage, precludes anticoagulant therapy.
3. A vena cava filter is indicated *secondarily* or prophylactically when:
   a) A patient who has had an embolus or active thrombophlebitis of the pelvic or leg veins requires either celiotomy for another surgical lesion or pulmonary embolectomy,
   b) There has been extensive trauma to the vena cava, iliac or pelvic veins during an abdominal or pelvic procedure,
   c) Recurrent emboli have occurred despite caval ligation.
4. Ligation of the vena cava is indicated when:
   a) Multiple small pulmonary emboli have occurred leading to incipient pulmonary hypertension or cor pulmonale,
   b) Emboli have occurred secondary to septic pelvic or peripheral thrombophlebitis, or in the presence of intraabdominal infection,
   c) Recurrent emboli have occurred after partial caval interruption.

Operative Technic (Figs. 1, 2, & 3)

As currently practiced, the abdomen is entered through a right upper quadrant transverse incision. After exploration of the abdominal cavity, a generous Kocher maneuver is performed, the duodenum is retracted medially, and the vena cava is exposed over a distance of approximately 7 cm. (Fig. 1). The right ovarian (or spermatic) vein is identified as it enters the vena cava or right renal vein and is doubly ligated and divided. If lumbar veins enter the vena cava at this level, they are ligated in similar fashion. The vena cava is encircled with a plastic tape to facilitate mobility and an angled atraumatic vascular clamp is applied tangentially to the vena cava in the anterior-posterior position at a point just below (caudad to) the renal veins (Fig. 2). A second vascular clamp is similarly placed across the vena cava 3 cm. more caudally, taking care to strip the vena cava of blood as it is being placed. The grid-like filter is constructed of teflon-impregnated dacron sutures of 4–0 size which have vascular needles on both ends. Starting near the posterior wall of the vena cava, at a point just caudal to the uppermost vascular clamp, a series of mattress sutures is placed across the vena cava from right to left. The individual suture strands are placed 2 or 3 mm. apart, and each succeeding suture is placed slightly more anterior and slightly more caudal than the preceding one until the anterior wall is reached, thereby creating a tangential plane for the completed filter. Ordinarily, five to eight mattress sutures are required to complete the filter. None of the sutures is tied until all have been satisfactorily positioned. The vascular clamps are then removed, permitting the vena cava to become normally distended. Starting with the most posterior suture, each is tied firmly but care is taken not to constrict the vena cava significantly. This is facilitated by maintaining counter tension on the free loop of the suture with a nerve hook or the tip of a hemostat while the knots are being tied.

Before terminating the procedure, the left ovarian (or spermatic) vein is ligated (Fig. 3). This is accomplished by dissecting retroperitoneally along the lower border of the left renal vein until the gonadal vein is reached at its point of entry into the renal vein. The peritoneal attachments of the duodenum are then restored and the abdominal wound is closed in appropriate fashion.

In our original description of this procedure, the filter was constructed with a continuous suture rather than by interrupted sutures. Although this proved satisfactory in most instances and has been used in the alternate procedure described below, it is somewhat more difficult to adjust the tension of the individual strands when the continuous technic is used. This may result in greater constriction of the vena cava than is desirable unless care is taken to avoid it.

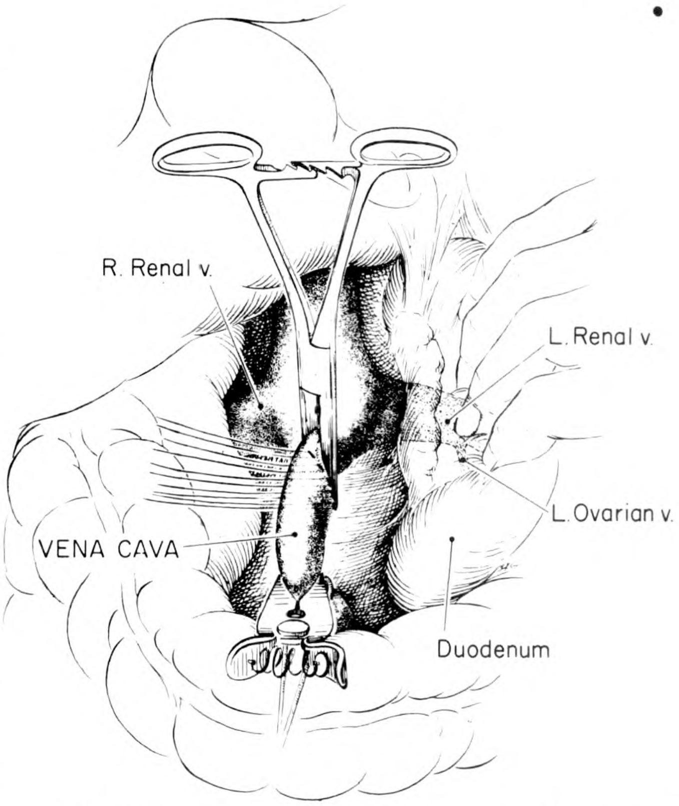


FIG. 2. Construction of vena cava filter at infra-renal level with interrupted vascular sutures.

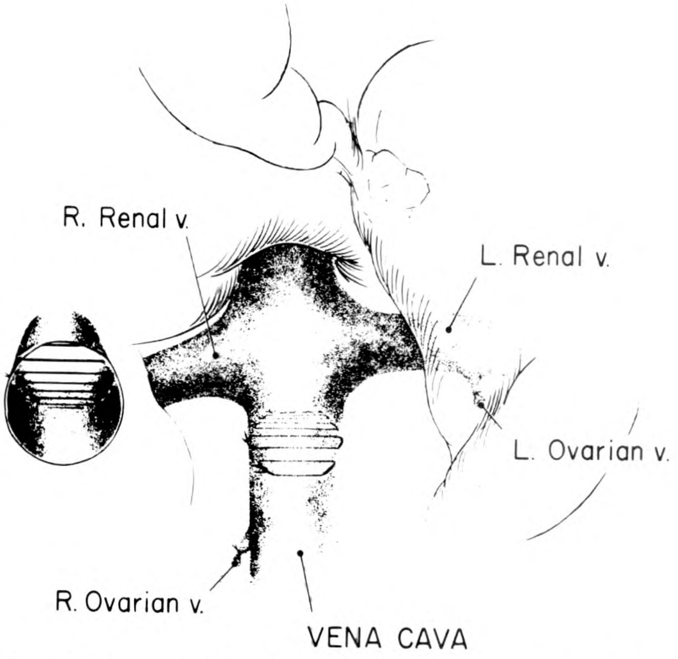


FIG. 3. Vena cava filter has been completed and both ovarian veins have been ligated.

Alternate Technic (Fig. 4)

One of us (ROK) further modified the operative technic and has employed it in most of the 43 patients in the St. Joseph Hospital subseries (Fig. 4). The hepatic flexure of the colon as well as the duodenum is mobilized and reflected medially. A double filter is constructed, the individual grids of which are placed approximately 3 cm. apart. The placement of the sutures has been facilitated by the use of a double-bladed vascular clamp which was especially designed for this purpose as depicted in Figure 4.

Anticoagulant Therapy Postoperatively

The use of anticoagulants in these patients in the immediate postoperative period was dictated largely by the status of their antecedent thrombophlebitis. Anticoagulant therapy was not administered as a routine and was not employed in those patients in whom the filter had been placed prophylactically or who had demonstrated an intolerance to anticoagulant drugs. There is no evidence to suggest that there was a greater incidence of occlusion of the filter in those patients who did not receive anticoagulants. External elastic supports to the legs were advised only in the presence of acute thrombophlebitis or demonstrable edema. Patients with acute phlebitis were kept at bed rest with the foot of the bed elevated 15° during the acute phase of the process and heparin therapy was administered intravenously in sufficient dosage to prolong the Lee-White clotting times to twice their normal values. Warfarin therapy was begun on the fifth to seventh postoperative day and the dosage adjusted to a prothrombin time of approximately twice normal or to 25–30% on the Quick scale. When this level had been attained, heparin was discontinued and warfarin continued during the remainder of the postoperative stay and for an additional 6–12 weeks following discharge from the hospital. Some hemorrhagic complications were noted in the early postoperative period but none of these was of major consequence.

Those patients who manifested peripheral edema of the legs were measured for Jobst stockings when the edema had become stationery at bed rest. The elastic support hose were continued during the follow-up period as long as they were needed and patients were permitted to abandon them if and when clinical edema no longer was present.

Results

A total of 112 patients who had intraluminal caval filters constructed during the years 1957–1972 were available for study. The operations were performed for pri-

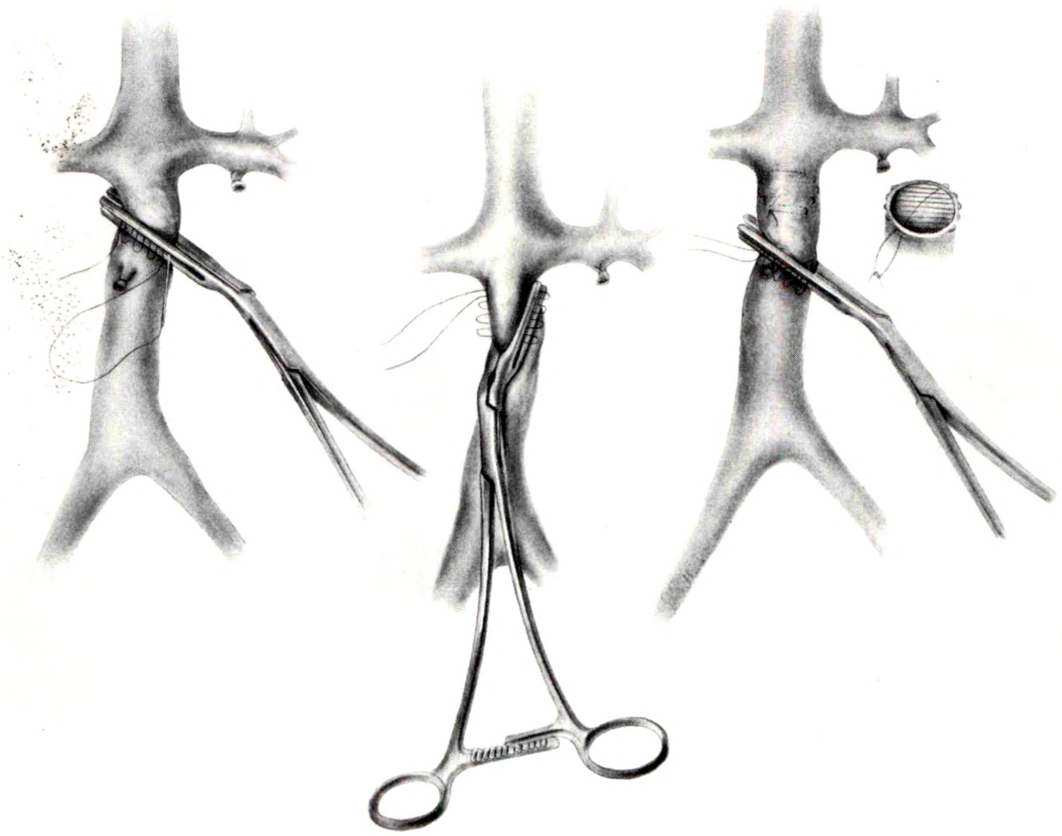


FIG. 4. Alternate technic (method of R. Kraft). A double filter is constructed with continuous suture utilizing a double-bladed vascular clamp.

TABLE 2. *Length of Postoperative Follow-up*

	No. of Patients
<1 year	47
1–2 years	24
2–3 years	8
3–4 years	7
>4 years	16
	102
(Range one month to 153 months)	

mary indications in 81 patients and for secondary ones in 31. Of these, 102 patients survived the immediate postoperative course. The duration of the follow-up period ranged from one month to 153 months (Table 2).

Mortality (Table 3)

No deaths occurred in the operating room during the procedures. Ten deaths occurred within 30 days of operation for an overall early postoperative mortality of 9.0%. Of these deaths, however, only four (3.6%), occurred in patients who were advised operation for one of the primary indications listed in our operative criteria. In the remaining six (5.4%), the filter was placed during the course of an operation which was indicated by another catastrophic illness. The causes of death in these ten patients are listed in Table 3.

An additional 17 patients (15.2%) have died during this study period at intervals of 1 month to 153 months following operation. Death in each instance was attributable to primary cardiac, neoplastic or other degenerative disease. In no instance was death attributable to recurrent pulmonary infarction, as evidenced by either clinical or autopsy findings.

Recurrent Pulmonary Emboli (Table 4)

All patients have been kept under surveillance and follow-up diagnostic studies carried out when indicated. All were subjected to periodic clinical examinations and chest x-rays for at least 1 year postoperatively. In recent years, lung scans and blood gases have been obtained whenever a suspicion of recurrent pulmonary infarction has arisen; eleven patients have had one or several scans. Pulmonary angiograms have been obtained in only five patients but phlebograms of the inferior vena cava have been obtained during the follow-up period in 32 patients.

Under this follow-up program, 18 patients (16.0%) were suspected of having had a recurrent non-fatal pulmonary embolus on the basis of their symptomatology (Table 4). Following objective study, however, the presence of a pulmonary parenchymal abnormality could be documented in only 11 (9.8%) of them.

TABLE 3. *Mortality*

Total Number of Patients	112	100%
Deaths in Operating Room	0	0
Cause of Deaths Within 30 Days of Operation		
IVC filter done for primary indication		
Myocardial infarction (EKG confirmed)	1	
Congestive heart failure	1	
Generalized coagulopathy	1*	
Unexplained—coronary occlusion ?, embolus ?	1	
	4	3.6%
IVC filter done for secondary indication		
Cardio-pulmonary, after pulmonary embolectomy	2*	
Complications of pelvic exenteration	2*	
Myocardial infarction after A-F by-pass	1*	
GI hemorrhage and renal failure after colectomy	1	
	6	5.4
Cause of Deaths after 30 Days (one month to 153 months)		
Cardiac disease	5***	
Neoplasm	6**	
C.V. accident	1*	
Other	5*	
Pulmonary embolus	0	
	17	15.2%
	27	24.2%

* Autopsy in 11 patients

Autopsies were performed in four of these 11. A previously unsuspected carcinoma of the lung, and not infarction, was found to be the basis for the abnormal scan in one patient. Although recurrent pulmonary emboli were found at autopsy in three others, these were fully documented as having originated within the right atrium, greater azygous vein and left spermatic veins, respectively. This latter finding has led us to conclude that it is as important to interrupt the spermatic veins in men as it is the ovarian veins in women during the course of vena caval interruption. Failure of the filter

TABLE 4. *Recurrent Pulmonary Emboli*

		No.	%
Total Number of Patients		112	100%
Post-filter Emboli Suspected		18	16%
Failure of Filter Proved			
Symptoms + positive lung scan	3		
Symptoms + positive pulmonary angiogram	2		
Symptoms + positive scan and angiogram	2		
		7	6.2%
Failure of Filter not Proved			
Symptoms but lung scan(s) normal	3		
Symptoms but pulmonary angiogram normal	1		
Symptoms but chest X-rays normal	3		
Autopsy evidence of other routes for emboli	3		
Autopsy evidence false positive scan (carcinoma)	1		
		11	9.8%

to prevent recurrent emboli must be accepted in the remaining seven patients (6.2%).

As noted in Table 3 there were no proved fatal recurrent pulmonary emboli in this series of patients. One patient, who was also reported in our previous clinical report, however, died in another hospital following the filter procedure under circumstances which raised a suspicion of either acute myocardial infarct or pulmonary embolus. Autopsy was refused, however, and the clinical findings were too sparse to support a valid diagnosis of the cause of death.

Postoperative Extremity Morbidity

One hundred two of the 112 patients survived operations and the first postoperative month and were available for follow-up studies. The nature of the post-filter sequelae which these patients developed in their legs was evaluated clinically and venograms obtained when possible. No attempt was made to categorize the extent of edema—they either had identifiable edema or they did not have edema.

A. *Clinical Edema (Table 5)*

Thirty-seven patients (36.3%) had clinically demonstrable edema of the legs at some time during their postoperative courses. The edema was thought to be related to operation or to the antecedent phlebitic process in 27 (26.5%) of these. Ten patients (9.8%) had cardiac or renal disease which clinically was thought to be responsible for, or contributory to, the edema. All patients with edema were advised to wear elastic support hose and the edema was easily controlled in most of them. The remaining 65 patients (63.7%) had no evidence of clinical edema and were not required to wear support hose.

The edema was ipsilateral in eight patients and was thought to be related to the antecedent thrombophlebitis. This premise was supported in general by venographic studies which revealed caval patency in five of the six patients studied. Contralateral edema developed in two patients and was considered to be a manifestation of probable caval obstruction. This was confirmed by venography in the one patient who submitted to the study.

TABLE 5. *Postoperative Edema of Legs (Patients Studied = 102/112)*

	Clinical Edema		IVC Venogram			
	No.	%	No. Studied	No. Occluded	No. Patent	% Patent
Ipsilateral	8	7.8	6	1	5	83.3
Contralateral	2	2.0	1	1	0	0.0
Bilateral						
Venous disease only	17	16.7	7	5	2	71.4
Associated cardiac or renal disease	10	9.8	5	0	4	80.0
	37	36.3	19	8	11	58.0

Bilateral edema was manifested by a total of 27 patients (26.5%). In 17, the edema was believed to be related to either primary involvement of the vena cava by thrombophlebitis, or by occlusion of the filter by thrombosis at the filter site or by entrapment of a major embolus. Venography confirmed the presence of caval occlusion in five of the seven patients studied but did not provide precise information concerning the cause of the caval obstruction.

Four of the nine patients with bilateral edema and associated congestive heart disease underwent venography and the vena cava was proved to be patent in all four. It was found to be occluded, however, in the one patient who had associated renal disease.

In summary, caval patency was demonstrated by venography in five of the seven patients who had unilateral edema. The demonstration of caval patency in six of the 12 patients with bilateral edema who were studied is more significant. Of the total group of 19 patients with clinical edema who submitted to venography, caval patency was found to have been preserved in 11 of them (58%).

B. *Recurrent Thrombophlebitis*

Sixteen patients (15.7%) developed recurrent thrombophlebitis at some time during the postoperative courses. The process was ipsilateral to the original disease in seven and generally represented reactivation of the original process. Contralateral thrombophlebitis developed later in five patients and bilateral thrombophlebitis in four. Although these were presumed to be related to caval obstruction, this was not uniformly true as subsequent venograms revealed caval patency in several. One patient with a hypercoagulable syndrome developed phlegmasia cerulea dolens in the immediate postoperative period. He was subjected to ilio-femoral thrombectomy and survived after a prolonged convalescence.

C. *Leg Ulcers*

Four patients (3.9%) had stasis ulcers during the follow-up period. The ulcers had been present prior to caval interruption in two of the patients and developed after trauma to the ankle in another patient. Two responded to conservative measures and two required excision and split-thickness skin grafts to effect healing.

D. *Stasis Dermatitis*

Two patients (1.9%) developed stasis dermatitis in edematous extremities and did not have skin ulceration. Both were readily managed by support hose.

E. *Cumulative Extremity Morbidity*

As multiple postphlebitic or postoperative leg sequelae may occur in the same patient, the ratio of patients who do, or do not, experience definable postoperative complications of the extremities is most significant. In this series, 44 (43.1%) of the patients had one or several of the sequelae listed. The remaining 58 (56.9%) were entirely symptom-free and did not require elastic stockings or other supportive measures in their postoperative management.

Filter Patency (Table 6)

Data regarding filter patency were obtainable in 45 patients (40.1%) by phlebography, autopsy or reoperation. The filter was found to be patent in 32 of these patients (71%) and occluded in 13 (29%).

Although organized emboli were found to have been arrested by the filter in three patients examined at autopsy, in no instance did we find evidence at autopsy or by caval venography that fresh thrombi had developed at or above the filter site. Pulmonary scans or arteriograms provided evidence of small, peripheral pulmonary emboli in seven patients but none of these was fatal. This finding had been anticipated from our initial animal studies and had led us to establish the criterion advising total caval ligation in those patients who experience repeated small pulmonary emboli, either before partial caval interruption or after it. Secondary caval ligations were performed in five of these seven patients who had previous caval filters. However, three of them continue to have intermittent chest pain of the type which led to their secondary caval ligations.

The postoperative venograms have revealed other interesting findings in a number of patients. In one instance, a dual vena cava was encountered. This had not been recognized at the time the filter had been placed in the right-sided vena cava. This patient has had several transient episodes of chest pain but pulmonary radiograms and scans have been negative. The left-sided vena cava has not been interrupted. Although this would seem to justify routine preoperative contrast studies of the vena cava prior to caval interruption, double vena cavae occur so rarely that this is not practical. It has influenced us, however, to look for an accessory left-sided vena cava while exposing the left gonadal vein at operation; none has as yet been identified intraoperatively. The incidence of dual cavae is reported to be 2.2%.[22]

The development of large retroperitoneal collateral veins in response to total caval ligation has been well emphasized by others. We, too, have observed this in patients studied by caval venography following total ligation of the cava. Two patients during this time interval experienced recurrent emboli following total caval ligation and a subsequent cavagram demonstrated large collaterals entering the inferior vena cava below the renal veins. Caval filters were placed in both patients at the infra-renal level at a subsequent operation. However, one of them subsequently died following pulmonary embolectomy for a massive embolus which was proved at autopsy to have arisen in the right heart. In no instance in which patency of the vena cava has been maintained and visualized postoperatively has a similar development of collateral venous channels been demonstrated.

TABLE 6. *Patency/Occlusion Rates (Patients Studied = 45/112)*

	Patent	Occluded	Total Studies
IVC Venogram	21	11	32
Autopsy	8	2	10
Reoperation	3	—	3
Total	32 (71%)	13 (29%)	45 (100%)

We have shunned placing the caval filter at the suprarenal level because of concern over the possible renal complications if embolic occlusion of the vena cava should occur subsequently at this level. Placement of the filter at the supradiaphragmatic level would have obvious advantages during pulmonary embolectomy. The following case presentation illustrates that suprarenal placement may be accomplished safely and advantageously under some circumstances and perhaps should be considered more frequently.

Case Report

A 45-year-old man underwent left renal transplant from a sibling donor in the University of Michigan Hospital in June 1967. He developed minimal signs and symptoms of thrombophlebitis in the right leg 2 days prior to re-admission to the hospital in September 1968 with a massive pulmonary embolus. Pulmonary embolectomy was successfully accomplished at that time. A complementary filter was placed in the vena cava cephalad to the transplanted renal vein. The patient survived and a venogram 1 month later revealed patency of the filter and renal vein though there was thrombotic obstruction of the iliac veins and distal vena cava. Three years later (November 1971) the patient had good renal function and minimal bilateral edema of the legs.

Discussion

The vena cava filter was conceived, tested in the experimental laboratory and subjected to long-term clinical trial in an effort to test the validity of the principle of caval filtration in the prevention of recurrent pulmonary emboli. If this principle is to be deserving of final acceptance by the surgical community, it must be shown to have distinct advantages over that of permanent caval ligation.

Our primary objective in this study has been directed toward a long-term longitudinal evaluation of the caval filter model which we introduced and have attempted to appraise critically. Although simple in design, it provides a comparatively "pure" form of partial caval interruption. The filter can be placed accurately at the optimum position in the vena cava, *i.e.*, just caudal to the renal veins, and does not alter significantly the hemodynamics of the vena cava. There are no hazards of migration, late perforation of the wall of the vena cava or erosion of surrounding structures. Unless it becomes obstructed, the filter does not in itself stimulate the development of large collateral venous channels which have been shown to provide potential pathways for the transit of emboli to the lungs following total caval ligation.

The fact that we have accepted only 112 patients for caval filtration in this 15-year time span is a reflection of our relative conservatism in advising operative intervention. We have placed initial dependence upon anticoagulant therapy in our management of thromboembolic disorders, as have many, but not all, investigators in this field. At the outset of this study, we were influenced in this decision by the favorable experience which was being amassed by a multidisciplinary team of colleagues in the University of Michigan Hospital who devoted themselves to a long-term prospective study of the role of anticoagulant therapy in thromboembolism. The results of this 20-year study were published subsequently by Coon *et al.*[6] Their data showed that recurrent pulmonary emboli occurred in 4.9% of patients who were effectively anticoagulated within the hospital after an initial embolic episode; 1.3% of these proved to be fatal. Although an additional mortality rate of 0.7% due to pulmonary embolism occurred within 3 months after release from the hospital if anticoagulant therapy was discontinued then, this late mortality rate was subsequently reduced also by extending the period of anticoagulation an additional 6–12 weeks.

The studies of Sevitt and Gallagher,[39] Barrett and Jordan,[5] Salzman *et al.*[36] and Skinner and Salzman[40] provided evidence that anticoagulant drugs are important in the prevention and management of thromboembolism. The total mortality rate of 2.05% from pulmonary embolism reported by Coon compares with the mortality rate of 3.6% which we have observed in patients who were accepted for caval filtration because of one of our primary indications. Although we have been strongly tempted to extend our indications for operations at various times during the 15-year course of this study, we have adhered to the protocol.

The only additional indication which we feel is warranted at the present time is provided by the occasional patient who has survived a massive embolus with the loss of a critical degree of pulmonary perfusion. As even small recurrent emboli might prove fatal, caval interruption should be considered seriously under these circumstances without subjecting the patient to a preliminary trial of anticoagulant therapy.

The criticism has sometimes been made that the transperitoneal approach which we advocate introduces a greater operative hazard than does the more rapid and less demanding technic of caval ligation by the retroperitoneal approach. Our mortality data do not bear this out. By the same token, we consider ligation of both gonadal veins to be an important element in the procedure; ligation of the left ovarian or spermatic vein is precluded by the retroperitoneal exposure.

Early in our experience an occasional patient was subjected to caval ligation instead of filtration because of a presumed difference in operative hazard, but this premise was soon abandoned by us as our experience mounted. Although some of our immediate colleagues have continued to advise total ligation under such circumstances, no patient in our personal series is rejected for the filter because of age or degree of operative risk if the other criteria for operation have been met.

The overall mortality within 1 month of operation in this series, including those who were critically ill because of their primary disease, was 9.0%. This compares favorably with the mortality rate of 9.19% reported by Ochsner *et al.*[30] within two weeks of caval ligation through a retroperitoneal approach. Krause *et al.*[18] reported an operative mortality of 5.5% following caval ligation and deMeester *et al.*[7] reported a 13% mortality following caval plication by the Spencer method. Adams *et al.*,[3] in a comparative study of the two methods, reported an in-hospital mortality rate of 13% following caval ligation and 8% following partial interruption.

In an occasional patient, acute obstruction of the vena cava may reduce the venous return to the heart acutely to a critical level and result in hypotension and cardiac arrest on the operating table. Following an episode of this nature early in our experience,[10] we have advocated the precaution of test-clamping the vena cava before ligating it. If the patient manifests hypotension or cardiac arrhythmia during the test, partial interruption should be carried out rather than ligation. Adams *et al.*[3] also reported intra-operative deaths in two patients who developed shock and irreversible cardiac arrest immediately following total caval ligation.

These data do not indicate a clear superiority of one method over another as regards operative mortality. Many of the patients who require caval interruption are critically ill and present a severe challenge in their intraoperative and postoperative management. Some inevitably die early as a result of the primary disease which predisposed them to the thromboembolic insult. For these reasons, the transvenous methods have great appeal as potentially they should be capable of reducing the operative risks inherent in the open operations.

It is also extremely difficult to compare data concerning the incidence of recurrent pulmonary emboli following the different methods as the clinical detection of recurrent pulmonary emboli remains an enigma despite recent refinements in diagnostic technics. The development of pulmonary scanning, blood gases technics and pulmonary angiography have provided important, new dimensions in diagnosis. Although they, too, may be subject to misinterpretation, it is becoming increasingly apparent that none of the caval interruption procedures, either partial or total, provide complete protection against recurrent pulmonary infarction. Gurewich *et al.*[15] reported an incidence of 20% recurrent pulmonary embolism after ligation of the inferior vena cava. Piccone and associates[33] in a carefully documented study of 72 patients reported an incidence of recurrent emboli of greater than 50% following caval ligation. Filler and Edwards,[12] Parrish *et al.*[31] and Piccone,[33] among others, have called attention to the large venous collaterals which develop following caval ligation and through which emboli may reach the pulmonary circulation. Adams *et al.*[3] reported an 8% incidence of recurrent emboli after partial caval interruption and an identical incidence of 8% following total ligation. There was, however, one fatal embolus in the ligation series. Ochsner *et al.*[30] observed a 4% incidence of recurrent emboli after partial interruption procedures in 28 patients and no recurrent emboli following caval ligation in 286 patients.

Again, it is difficult to ascribe clear-cut superiority of one method over another as regards prevention of recurrent pulmonary emboli. Our documented incidence of 6.2% recurrent emboli due to filter failure is consistent with that reported by Adams *et al.* for both ligation and partial interruption, less than that reported by Gurewich and Piccone for ligation, but greater than that reported by Ochsner. It is perhaps significant, however, that in no instances have emboli originated *de novo* at the filter site, whereas contrary findings were reported by de-Meester *et al.*[7] following caval plication. The fact that large venous collaterals do not develop in those patients (71%) who maintain patency of the filter is also significant.

The development of recurrent chest pain following caval interruption is distressing to the patient and presents an enigma to the surgeon. Although secondary ligations were performed in five of our patients after apparent failure of the filter to protect the patient from recurrrent emboli, three of these patients have continued to experience intermittent episodes of chest pain. Bolstered by our increasing confidence that the filter does block potentially fatal emboli, we have adopted a more conservative attitude in the management of patients with presumed recurrent emboli following caval filtration unless the episodes are repetitive and objective evidence of pulmonary infarction is obtainable.

Although the placement of a double filter, as described in our alternate procedure, should theoretically afford a greater degree of protection than does a single filter, it is difficult to establish such superiority objectively. Recurrent small emboli were noted following both technics with approximately equal frequency and both appear to have offered complete protection against fatal emboli. The double-bladed vascular clamp, which was developed specifically for this procedure (ROK), facilitates the technical maneuvers required in constructing the filter. It is not essential to the success of the operation, however, as other atraumatic vascular clamps are satisfactory.

Our data indicate that the patients in this study group experienced fewer and less bothersome postoperative sequelae in their lower extremities than have those reported in most series following caval ligation. Although it is true that most patients with postligation edema of the legs can be successfully managed by early elevation and by the assiduous use of elastic support hose, some patients—particularly those who are intellectually or economically disadvantaged—may present a serious challenge in their rehabilitation. It would seem more appropriate to prevent edema and stasis complications if possible. The low incidence of edema from all causes (36.3%) and the total freedom from extremity morbidity experienced by a majority (56.9%) of these patients is probably the most significant finding in this study.

As a result of these observations, we are convinced of the validity of the filter principle in the management of patients with thromboembolic problems. Although these data are derived from our experience with one specific procedure, *i.e.*, the vena cava filter, the study has pertinence to other partial interruption procedures as well.

Within recent years, a variety of interesting transvenous technics have been introduced which permit caval interruption, partial[14,32] or complete-temporary[20,47] or permanent.[17] These methods hold exciting promise for the future as potentially they can be utilized in seriously ill patients without subjecting them to the risk of general anesthesia and celiotomy. While we strongly support the continuing investigation and critical appraisal of these various devices, we will look with greatest interest to the development of a clinically-acceptable method of effecting partial caval interruption by the transvenous route. The methods proposed by Eichelter,[11] Pate[32] and Greenfield[14] currently appear promising in this regard.

The umbrella filter of Mobin-Uddin is being subjected to energetic clinical trial at present but, because of its reportedly high occlusion rate,[13,25] will probably serve best as a method of producing total rather than partial caval interruption. None of the transvenous methods proposed to date offer protection against emboli arising in the ovarian or spermatic veins, a deficiency which invites further investigation.

Summary and Conclusion

1. In a 15-year clinical experience with the vena cava filter,
   a) There were no deaths proved to be due to recurrent pulmonary emboli.
   b) Recurrent non-fatal pulmonary emboli were suspected clinically in 16% of all patients. Of these, only 6.2% represented filter failures. Documented emboli reached the lungs through unprotected venous channels in 2.6%. The diagnosis of recurrent pulmonary infarction could not be documented objectively in the remaining 7.2%.
   c) The incidence of postoperative edema of the extremities from all causes was 36.3% and 56.9% of patients were totally free of extremity morbidity.
   b) No iatrogenic thrombi were identified at the filter site.
2. The principle of partial interruption of the inferior vena cava is therapeutically valid and useful in the management of thromboembolism.
3. The transvenous methods of effecting caval interruption merit continuing evaluation. In the authors' opinions, those which are designed to maintain caval patency are potentially most desirable.

Acknowledgment

The authors gratefully acknowledge the assistance of the George P. Pilling & Son Company in the development of the double-bladded atraumatic vascular clamp utilized in this study.

References

1. Adams, J. T. and DeWeese, J. A.: Experimental and Clinical Evaluation of Partial Vein Interruption in Prevention of Pulmonary Emboli. Surgery, **57**:82, 1965.
2. Adams, J. T. and DeWeese, J. A.: Partial Interruption of the Inferior Vena Cava. Surg., Gynecol. Obstet., **123**:1087, 1966.
3. Adams, J. T., Feingold, B. E. and DeWeese, J. A.: Comparative Evaluation of Ligation and Partial Interruption of the Inferior Vena Cava. Arch. Surg., **103**:272, 1971.
4. Barkett, V. M., Wright, R. and Greenfield, L. J.: Plication of the Inferior Vena Cava by a New Channeling Prosthesis. Am. J. Surg., **118**:981, 1969.
5. Barrett, D. W. and Jordan, S. C.: Anticoagulant Drugs in Treatment of Pulmonary Emboli. Lancet, **1**:1309, 1960.
6. Coon, W. W., Willis, P. W. and Symons, M. J.: Assessment of Anticoagulant Treatment of Venous Thromboembolism. Ann. Surg., **170**:559, 1969.
7. DeMeester, T. R., Rutherford, R. B., Blazek, J. V. and Zuidema, G. D.: Plication of the Inferior Vena Cava. Surgery, **62**:56, 1967.
8. DeWeese, M. S. and Hunter, D. C., Jr.: A Vena Cava Filter for the Prevention of Pulmonary Emboli. Bull. Soc. Internat'l Chir., **17**:17, 1958.
9. DeWeese, M. S. and Hunter, D. C., Jr.: A Vena Cava Filter for the Prevention of Pulmonary Embolism—A Five-Year Clinical Experience. Arch. Surg., **86**:852, 1963.
10. DeWeese, M. S. in discussion of reference #9.
11. Eichelter, P. and Schenk, W.: Prophylaxis of Pulmonary Embolism. Arch. Surg., **97**:348, 1968.
12. Filler, R. M. and Edwards, E. A.: Collaterals of the Lower Inferior Vena Cava in Man Revealed by Venography. Arch. Surg., **84**:10, 1962.
13. Fullen, W. D., McDonough, J. J. and Altemeier, W. A.: Clinical Experience With Vena Cava Filters. Arch. Surg., **106**:582, 1973.
14. Greenfield, L. J., McCurdy, J. R., Brown, P. P. and Elkins, R. C.: A New Intracaval Filter Permitting Continued Flow and Resolution of Emboli. Surgery, **73**:599, 1973.
15. Gurewich, V., Thomas, D. P. and Rabinov, K. R.: Pulmonary Embolism after Ligation of the Inferior Vena Cava. N. Engl. J. Med., **274**:1350, 1966.
16. Homans, J.: Deep Quiet Venous Thrombosis in the Lower Limb. Surg., Gynecol. Obstet., **79**:70, 1944.
17. Hunter, J. A., Sessions, R. and Buenger, R.: Experimental Balloon Obstruction of Inferior Vena Cava. Ann. Surg., **117**:315, 1970.
18. Krause, R. J., Cranley, J. J., Hallaba, M. A. S., Strasses, E. S. and Hafner, C. D.: Caval Ligation in Thromboembolic Disease. Arch. Surg., **87**:184, 1963.
19. Leather, R. P., Clark, W. R., Jr., Powers, S. R., Jr., Parker, F. B., Bernard, H. R. and Eckert, C.: Five-Year Experience with the Moretz Vena Cava Clip in 62 Patients. Arch. Surg., **97**:357, 1968.
20. Miles, R. M., Chappell, F. and Renner, O.: A Partially Occluding Vena Caval Clip for Prevention of Pulmonary Embolism. Am. Surg., **30**:40, 1964.
21. Miles, R. M. and Elsea, P. W.: Clinical Evaluation of the Serrated Vena Caval Clip. Surg., Gynecol. Obstet., **132**:581, 1971.
22. Milloy, F. J., Anson, B. J. and Cauldwell, E. W.: Variations in Inferior Caval Veins and in Their Renal and Lumbar Communications. Surg., Gynecol. Obstet., **115**:131, 1962.
23. Mobin-Uddin, K., Smith, P. E., Martinez, L. O., Lombardo, C. R. and Jude, J. R.: A Vena Cava Filter for the Prevention of Pulmonary Embolus. Surg. Forum, **18**:209, 1967.
24. Mobin-Uddin, K., McLean, R., Bolooki, H. and Jude, J. R.: Caval Interruption for Prevention of Pulmonary Embolism. Arch. Surg., **99**:771, 1969.
25. Mobin-Uddin, K., Collard, G. M., Bolooki, H., Robinson, R., Michie, D., and Jude, J. R.: Transvenous Caval Interruption with Umbrella Filter. N. Engl. J. Med., **286**:55, 1972.
26. Moretz, W. H., Naisbitt, P. F. and Stevenson, G. P.: Experimental Studies on Temporary Occlusion of the Inferior Vena Cava. Surgery, **36**:384, 1954.
27. Moretz, W. H., Rhode, C. M. and Shepherd, M. H.: Prevention of Pulmonary Emboli by Partial Occlusion of the Inferior Vena Cava. Am. Surg., **25**:617, 1959.
28. Moretz, W. H., Still, J. M., Jr., Griffin, L. H., Jennings, W. D. and Wray, C. H.: Partial Occlusion of the Inferior Vena Cava with a Smooth Teflon Clip: Analysis of Long-Term Results. Surgery, **71**:710, 1972.
29. Moser, K. M., Harsany, P. G., Harvey-Smith, W., Durante, P. L. and Guisan, M.: Reversible Interruption of Inferior Vena Cava by Means of a Balloon Catheter. J. Thorac. Cardiovasc. Surg., **62**:205, 1971.
30. Ochsner, A., Ochsner, J. L. and Sanders, H. S.: Prevention of Pulmonary Embolism by Caval Ligation. Ann. Surg., **171**:923, 1970.
31. Parrish, E. H., Adams, J. T. and Pories, W. J.: Pulmonary Emboli Following Vena Cava Ligation. Arch. Surg., **97**:899, 1968.
32. Pate, J. W., Melvin, D. and Cheek, R. C.: A New Form of Vena Cava Interruption. Ann. Surg., **169**:873, 1969.
33. Piccone, V. A., Vidal, E., Yarnoz, M., Glass, P. and LeVeen, H. H.: Late Results of Caval Ligation. Surgery, **680**:980, 1970.
34. Pualwan, F., Jones, G. E., Bruny, S. J. and Dale, W. A.:

Effects of Ligation of the Inferior Vena Cava with Absorbable Suture. Surg. Forum., 5:179, 1954.

35. Ravitch, M. M., Snodgrass, E., McEnany, T. and Rivarola, A.: Compartmentation of the Vena Cava with the Mechanical Stapler. Surg., Gynecol. Obstet., 122:561, 1966.
36. Salzman, E. W., Harris, W. H. and De Sanctis, R. W.: Anticoagulation for Prevention of Thromboembolism Following Fracture of the Hip. N. Engl. J. Med., 275:122, 1966.
37. Sensenig, D. M., Achar, B. G. and Serlin, O.: Plication of the Inferior Vena Cava with Staples. Am. J. Surg., 109: 679, 1965.
38. Sensenig, D. M.: Late Results of Plication of the Inferior Vena Cava with Staples. Am. J. Surg., 119:423, 1970.
39. Sevitt, S. and Gallagher, N. C.: Prevention of Venous Thrombosis and Pulmonary Embolism in Injured Patients. Lancet, 2:981, 1959.
40. Skinner, D. B. and Salzman, E. W.: Anticoagulant Prophylaxis in Surgical Patients. Surg., Gynecol. Obstet., 125: 741, 1967.
41. Spencer, F. C.: An Experimental Evaluation of Partitioning of the Inferior Vena Cava to Prevent Pulmonary Embolism. Surg. Forum, 10:680, 1960.
42. Spencer, F. C., Quattlebaum, J. K., Quattlebaum, J. K., Jr., Sharp, E. H., and Jude, J. R.: Plication of the Inferior Vena Cava for Pulmonary Embolism. Ann. Surg., 155: 827, 1962.
43. Spencer, F. C., Jude, J., Rienhoff, W. F. III, and Stonesifer, G.: Plication of the Inferior Vena Cava for Pulmonary Embolism. Long-Term Results in 39 Cases. Ann. Surg., 161:788, 1965.
44. Streuter, M. A. and Paine, J. R.: Temporary Occlusion of the Inferior Vena Cava Suggested as a Means of Treatment in Thromboembolism Requiring Cava Ligation. Surgery, 34:20, 1953.
45. Taber, R. E., Zikria, E., Hershey, E. A. and Lam, C. R.: Prevention of Pulmonary Emboli with a Vena Caval Clip. JAMA, 195:889, 1965.
46. Whitcomb, J. G. and Mostyn, M.: Experience with the Vena Cava Sieve Procedure for Prevention of Pulmonary Emboli. Am. J. Surg., 110:767, 1965.
47. Williams, R. W and Schenk, W. G., Jr.: A Removable Intracaval Filter for Prevention of Pulmonary Embolism: Early Experience with the Use of the Eichelter Filter in Patients. Surgery, 68:999, 1970.

DISCUSSION

DR. LESTER R. BRYANT (Lexington): Dr. DeWeese's results prove that partial interruption of the inferior vena cava is a valid approach to recurrent pulmonary embolism. Before Dr. Kazi Mobin-Uddin joined our Department nearly 3 years ago, we used the vena cava plication technic described by Dr. Frank Spencer. More recently, however, we have become converted to the transvenous method of vena caval interruption with employment of the Mobin-Uddin vena caval filter. Although this device has gained some unwarranted notoriety because of reported instances of migration to the pulmonary artery, it has proved to be very satisfactory, particularly for critically ill patients. The previous episodes of migration occurred with the 23 mm. filter. A 28 mm. filter is now available and migration has not occurred in 70 consecutive implantations.

Unfortunately, the transvenous filter devices have the disadvantage of thrombus formation on the distal surface, and occasionally on the proximal surface as well. We are presently evaluating a heparin-bonded filter in patients who are maintained on sodium warfarin for 3 months after implantation of the filter.

It would seem to us that an ideal method for management of recurrent pulmonary embolism might include a simple technic of transvenous insertion of a non-thrombogenic filter that could be removed easily at a later date. In the meantime, we feel that the 28 mm. filter offers significant advantages over operative approaches to the inferior vena cava with little risk of filter migration.

DR. LAZAR J. GREENFIELD (Oklahoma City): I, too, would like to congratulate Dr. DeWeese for a very valuable clinical report which makes the point of the value of continued patency of the vena cava.

To try to accomplish this goal, we have developed an approach which is transvenous and which does provide us with a technic of insertion under local anesthesia.

The filter is composed of stainless steel in a cone shape with very fine recurved hooks which allow fixation within the wall of the vena cava.

The principle of the cone is one that offers a distinct advantage making it possible to fill 70% of the depth of the cone with thrombotic material without introducing any significant impairment of flow through the vena cava. Only 49% of the cross sectional area would be blocked by filling of the cone to this point.

The plot of the relationship between filling and reduction of cross sectional diameter is shown on the slide.

The filter device is placed on a carrier catheter and inserted through a femoral venotomy. We have used this approach as a complement to the catheter technic for removal of pulmonary emboli. Thus, following use of the vacuum cup catheter to remove thrombotic material from the pulmonary arteries we can complete the procedure by insertion of the cone device.

One of the main advantages of the filter is the fact that there is no interruption of flow. When thrombotic material is trapped, there is little or no tendency for extension. In clinical experience with eight patients to date all of the cavae are patent.

The experimental results are quite encouraging because autogenous thrombi in animals can actually be seen to gradually resolve over a period of generally 3 to 6 weeks.

Complementary lung scans during this period of resolution do not show any evidence of pulmonary emboli by fragmentation, so that the additional benefit of preserved flow around the trapped thrombus would seem to offer the prospect of actual resolution of the thrombi.

The results are very preliminary so far, but we have had no evidence, either experimentally or in the patient population, that there is a tendency for propagation or extension of the thrombus even when an actual thrombus is trapped within the cone filter.

DR. M. S. DEWEESE (Closing): I want to thank both Dr. Bryant and Dr. Greenfield for their pertinent discussions as they represent two of the groups who are actively investigating transvenous methods of achieving caval interruption at the present time.

I still have some reservations about the non-operative methods, primarily because of the lack of long-term clinical data which will require more time to gather. The honesty of the reporting that has come out from the Kentucky and Oklahoma groups is certainly to be commended. The transvenous methods leave me a little bit anxious because of their failure to protect against emboli from the gonadal vessels. This is a concern which justifies further investigation.

We have been reticent to place the filters above the renal vein level, more from concern over possible embolic occlusion rather than of thrombosis of the filter itself. In our one patient who had undergone renal transplantation this worked out all right and if transvenous methods are perfected that maintain patency of the vena cava, there will be many obvious advantages.

Results of Carotid Endarterectomies for Transient Ischemic Attacks-Five Years Later

JAMES A. DeWEESE, M.D., CHARLES G. ROB, M.D., RICHARD SATRAN, M.D.,
DAVID O. MARSH, M.D., ROBERT J. JOYNT, M.D., DAVID SUMMERS, M.D.,
CAREN NICHOLS, BSN

*From the Departments of Surgery and Neurology,
University of Rochester Medical Center, Rochester,
New York 14642*

EASTCOTT, PICKERING, AND ROB reported successful reconstruction of a stenotic internal carotid artery for neurologic symptoms in 1954.[8] Since then several large series of operations on the carotid artery have been reported.[2,3,6,10,11,12] Carotid endarterectomies have been most frequently performed on patients with transient cerebral ischemic attacks (TIA). The reports of a collaborative study randomized into nonoperated and operated groups of patients with TIA suggest that carotid endarterectomies decrease late mortality rates.[1] In addition, patients who are operated upon have fewer TIA in the follow-up period.[9]

During the past 10 years 503 carotid endarterectomies have been performed at the University of Rochester, of which 285 were performed for TIA. It was possible to evaluate some of these patients for longer than 10 years. For the purposes of this presentation, however, we selected 103 consecutive patients operated upon for symptoms of TIA more than 5 years ago. The status of the patients at exactly 5 years following operation was analyzed. This retrospective study provides prognostic information useful in the evaluation of patients with TIA being considered for carotid endarterectomy.

Materials and Methods

The 103 patients in this study exhibited characteristics common to patients with symptomatic atherosclerotic lesions. There were 65 men and 38 women. The ages of the patients ranged from 46 to 80 years and 46% were in the 60–70 age range. Diabetes mellitus was present in 18% of the patients. Blood pressure recordings greater than 150/90 mm. Hg or a history of hypertension was observed in 45% of the patients. There was electrocardiographic evidence of arteriosclerotic heart disease in 24% of the patients. Aneurysysms or symptomatic peripheral arterial disease had been present in 17% of the group. Serum cholesterol determinations were performed on 57 patients, of whom 44 demonstrated levels greater than 275 mg./100 ml.

Symptoms (Table 1)

All of the 103 patients had histories of transient ischemic attacks (TIA). These attacks were transient episodes of local neurologic deficit which were rapid in onset and of less than 24 hours duration and from which recovery was complete. Ipsilateral eye symptoms, contralateral motor and sensory symptoms, or speech difficulties were observed in 85% of the patients. The ipsilateral eye symptoms consisted of scotomata, blurred vision, or transient blindness and occurred 39% of the time. Contralateral sensory or motor symptoms consisting of weakness, paralysis, numbness, or paresthesias occurred in 59% of the patients. Speech difficulties consisting of motor or expressive aphasia occurred in 17% of the patients. Speech symptoms were observed only if the involved arteries supplied the dominant cerebral hemisphere. Other symptoms such as dizziness, syncope, headache, seizures, and confusion occurred in some of the total group and only

---

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25–27, 1973.

Supported in part by U.S. Public Health Service Grand HE 07922-08 and The Waasdorp Laboratory for Stroke Research.

these nonclassic symptoms were observed in 15% of the patients.

The severity of the problem and the desire for immediate treatment by the majority of the patients are reflected in an analysis of the time of onset, time of the last, and frequency of TIA occurring prior to operation (Table 2). Thirty-nine per cent of the patients became symptomatic within 3 months of operation; 53% had multiple attacks at intervals of less than 3 weeks; 66% suffered the last attack within 1 month of operation. Only 13% of the patients had histories of single episodes and these single attacks occurred more than 6 months prior to operation in only 1% of the patients.

Bruits and Ophthalmodynamometry

The results of both a careful examination for bruits and ophthalmodynamometry were available in 54 patients (Table 3). Definite bruits were heard 84% of the time and ophthalmodynamometry was positive in 59% of the patients. However, ophthalmodynamometry was positive in the absence of a bruit 7% of the time. Therefore, one or both of the tests were positive in 91% of the examinations. This, of course, means that in 9% of the patients the diagnosis of arterial occlusive disease required angiography.

Electroencephalography

Electroencephalograms were obtained on 39 patients prior to operation and 41% of these patients demonstrated at least some minor abnormality on the tracing. These abnormalities usually consisted of intermittent mild to moderate focal slowing in the midtemporal and central areas.

Angiography

Angiograms were performed which visualized all four extracranial cerebral vessels in 63 patients prior to operation. Angiograms which visualized the involved vessels were obtained in another 18 patients. No angiograms were obtained in 19 patients who were operated on early in the study. In all that were operated upon there was a greater than 30% narrowing of the diameter of the internal carotid artery as seen on the AP and lateral angiogram, or by examination of the removed atherosclerotic core.

TABLE 1. *Neurologic Symptoms in 103 Patients with TIA*

Symptoms	TIA Only		% Patients	
Classic	88		85%	
Ipsilateral Eye		39		39%
Contralateral Motor or Sensory		61		59%
Speech		17		17%
No Classic Symptoms	15		15%	
Other				
Dizziness		20		19%
Syncope		12		12%
Headache		2		2%
Seizures		5		5%
Confusion		1		1%

TABLE 2. *TIA Prior to Operations in 103 Patients*

TIA	Number of Patients	Percentages
First		
0–3 mo.	40	39%
3–12 mo.	24	23%
>1 yr.	39	38%
Frequency		
q. 0–7 days	24	23%
q. 1–3 wks.	31	30%
q. 1–12 mo.	35	34%
Isolated		
<6 mo.	12	12%
>6 mo.	1	1%
Last		
0–7 days	36	35%
1–4 wks.	32	31%
1–12 mo.	34	33%
>1 yr.	1	1%

Operation

The operations were performed between January 1, 1961 and December 31, 1966.

A general anesthetic was used in 94 operations of which 7, early in the study, were accompanied by total body cooling to esophageal temperatures of 31–32 C. A local anesthetic was used in 11 operations. In most of the operations general anesthesia was used and an attempt was made to maintain the blood pressure at normotensive or even slightly hypertensive levels.

The operations were performed through a transverse incision along a skin crease at the level of the thyroid cartilage. The anterior facial vein was divided and the carotid bifurcation was mobilized—taking care to avoid injury to the hypoglossal nerve. A longitudinal arteriotomy was made over the atherosclerotic plaque beginning at the distal end of the common carotid artery and extending along the postero-lateral side of the internal carotid artery to the end of the palpable plaque. In some instances, the incision was initially made through only the adventitia and outer media to enable placement of staysutures and partial performance of the thromboendarterectomy before the vessels were occluded. Care was taken to remove all of the shreds of media and to carefully cut the atherosclerotic intima at the point where it fused with normal intima. Five thousand units of heparin were injected into the distal carotid artery after occlusion of the vessels and 50 mg. of protamine sulfate were given intravenously following closure of the arteriotomy. The total time of occlusion was less than 10 minutes in 11% of the opera-

TABLE 3. *Bruits and Ophthalmodynamometry*

Bruit	Ophthalmodynamometry	Number of Patients	Per cent
Present	Positive	28	52%
Present	Negative	17	32%
Absent	Positive	4	7%
Absent	Negative	5	9%
		54	100%

tions and greater than 20 minutes in only 5% so the usual time was between 10 and 20 minutes. Internal shunts were used on only two occasions when technical problems arose which prolonged the period of occlusion beyond 25 minutes. In four instances redundant artery was excised and an end-to-end anastomosis performed between the common carotid artery and the internal carotid artery. Small rubber tissue drains were left through stab wounds in the subcutaneous tissue for a period of 24 hours. No anticoagulants were used in the postoperative period.

Patients without complications were discharged from the hospital within 5 days of operation and were then seen periodically. It was possible to maintain direct contact with or confirm the death of 100% of the patients 5 years following operation.

Surgical Results

Early Clinical Results

Eighty-two (79%) of the patients were asymptomatic during the first 30 days following operation. Transient mild weakness of the opposite extremities beginning immediately after operation and lasting for 1 to 2 days was observed in 15% of the patients. At the end of this early follow-up period of 30 days, 94% of the patients were without neurologic symptoms or deficits. One death occurred and was related to a major cerebral infarction and myocardial infarction. There were six patients who demonstrated evidence of a definite cerebral infarction with worsening of neurologic status following operation, including the one death. Two of the patients were hemiplegic and aphasic and still showed dysarthria and hemiparesis on discharge from the hospital. One patient demonstrated slight but definite facial weakness. Another showed some arm weakness.

Minor complications were observed following three operations. One patient developed a wound hematoma which required evacuation. One patient developed a wound infection requiring drainage. Eighteen patients developed transient weakness of the tongue with deviation toward the operated side presumably secondary to traction on the hypoglossal nerve during operation.

Late Results

The late results recorded included mortality, neurologic status of the patients, and occurrence of other complications of generalized atherosclerosis.

Mortality

Thirty-five (34%) of the patients died within 5 years of operation (Fig. 1). The mortality rate during the first year was 10%. The mortality rate was 5 to 8% for each ensuing year. At the end of 5 years 68 (66%) of the patients were alive.

Myocardial infarctions were considered the cause of death of 24% of the patients of which one died in the hospital following operation (Table 4). In 17 of these 25 patients the diagnosis was supported either by a convincing clinical course, positive electrocardiogram, or an autopsy. The diagnosis of myocardial infarction must be considered only probable in the other eight patients who died at home, frequently suddenly, and on whom no autopsies were performed. Five patients died of strokes. One patient died from nephrosclerosis. Three patients died of cancer and one from other causes.

The overall mortality rate of 34% during 5 years was analyzed in relation to the preoperative status of the patient (Table 5). The mortality rate for patients 70 to 79 years of age was 52% as compared to 19% and 38%, respectively, for the 50 to 59, and 60 to 69 year age group. Thirty-nine per cent of hypertensive patients died and 30% of those without hypertension also died. There was a mortality rate of 56% in patients with atherosclerotic heart disease as compared to 27% when arteriosclerotic heart disease was not pres-

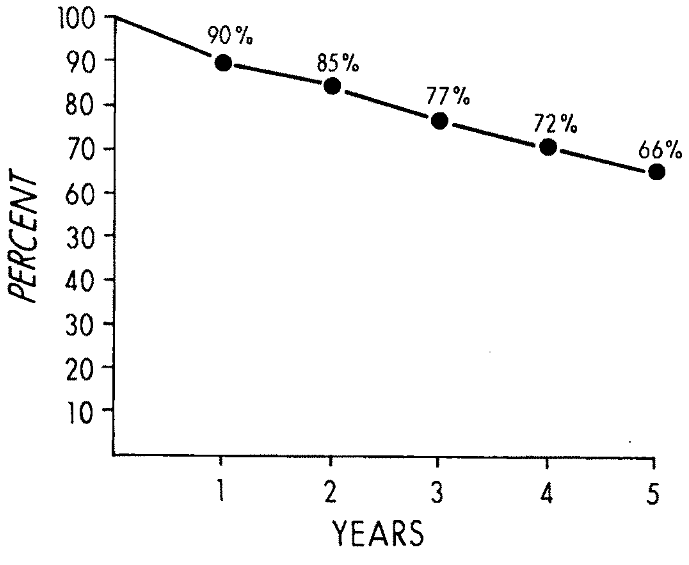


FIG. 1. Survival rate of 103 patients following carotid endarterectomy for TIA's.

TABLE 4. *Causes of Deaths*

	Number	%
Myocardial Infarction	25	24%
Cerebrovascular Accident	5	5%
Nephrosclerosis	1	1%
Cancer	3	3%
Pneumonia	1	1%
Total	35	34%

ent. Thirteen of 14 (93%) of the deaths in patients with arteriosclerotic heart disease were secondary to myocardial infarctions as compared to 12 of 21 (57%) of patients without arteriosclerotic heart disease. The mortality rate in patients with diabetes was 42% as compared to 32% in nondiabetics. Of the eight patients who preoperatively had both diabetes and arteriosclerotic heart disease, six died within 5 years.

Neurologic Status

The late neurologic status was first analyzed in regard to those symptoms and signs thought to be related to lesions of the carotid artery on which the operation was performed (Table 6). Seventy-eight of the 103 patients remained completely free of preoperative symptoms throughout their follow-up. Sixteen patients continued to complain of the same symptoms but they occurred less frequently and on only one occasion in four patients. These symptoms consisted of motor and sensory losses, dysphasia, or visual symptoms in only five patients. The other 11 patients were originally operated on with nonclassic symptoms such as dizziness, poor memory, seizures, or syncope.

Three of the 103 patients continued to complain of the same symptoms with the same frequency following operation. One patient continued to have seizures and another continued to complain of headaches and tremor—repeat angiograms demonstrated patent carotid reconstructions. The third patient continued to have intermittent episodes of amourosis, and hemiparesis. An angiogram demonstrated thrombosis of the reconstructed carotid artery. A second reconstruction was performed which also thrombosed.

Six patients were discharged from the hospital with significant persistent neurologic deficits which appeared soon after operation (Table 7). Three died and three lived at least 5 years. Three of the six demonstrated minimal deficits when last seen. One continued to have expressive aphasia which interfered with his profession as a priest but did not affect activities of daily living. Two patients demonstrated significant deficits which interfered with activities of daily living.

Eighty-eight of the 103 patients were operated on for "classic" symptoms of motor and sensory loss, dysphasia, or visual disturbances. Seventy-six of the 88, or 84%, had no neurologic complications and were relieved of their symptoms. Fifteen of the 103 patients complained only of nonclassic symptoms of dizziness, syncope, headache, seizures, or confusion. Only two of the 15, or 13%, were relieved of symptoms.

Twenty-four of the 103 patients developed new neurologic symptoms not considered to be related to lesions of the carotid artery operated on. Twenty-one patients complained of motor, sensory, speech, or visual symptoms. Three complained only of vertigo, ataxia, syncope, or dizziness. Thirteen patients complained only of transient symptoms. Eleven patients suffered completed strokes with residual deficits which were mild in five, moderate in four, and severe in two patients (Table 7). Angiograms were available on 15 of the 25 patients and significant lesions of the unoperated carotid artery were demonstrated in 12 patients (11 with TIA and 1 with a completed stroke). Carotid endarterectomies were performed on these 12 patients.

A total of 17 of the 103 patients demonstrated significant lesions of their opposite carotid arteries and endarterectomies were performed within 5 years of first operation. This includes the above mentioned 12 symptomatic patients as well as five patients with asymptomatic carotid lesions. Seventy-one per cent of the second operations were performed within 1 year of first operation.

Five patients died of strokes. One patient developed an infected false aneurysm which required ligation of the carotid artery which caused hemiplegia and death 7 months following original operation. One patient had fewer symptoms following operation but died suddenly of a stroke 4 months later. Two patients who

TABLE 5. *Mortality Rate as Related to Preoperative Status*

	No.	Deaths	Mortality Rate %
Age–Years			
26–49	3	0	0%
50–59	29	5	18%
60–69	47	18	38%
70–79	23	12	52%
80–89	1	0	0%
Hypertension			
Present	46	18	39%
Absent	57	17	30%
Arteriosclerotic Heart Disease			
Present	25	14	56%
Absent	78	21	27%
Diabetes			
Present	19	8	42%
Absent	84	27	32%
Arteriosclerotic Heart Disease and Diabetes			
Present	8	6	75%

TABLE 6. *Late Neurologic Status Related to Operated Carotid Artery*

		Late Neurologic Symptoms							
			Fewer		Same		Early Worsening—Late Neurologic Deficits		
Category	Number of Patients	None	Classic	Nonclassic	Classic	Nonclassic	None or Mild	Moderate	Severe
Died	35	23	3	4	0	2	1	1	1
Lived	68	55	2	7	1	0	2	0	1
Total	103	78	5	11	1	2	3	1	2

had early worsening following operation with moderate and severe residual deficits, died following further progression of neurologic deficits, 26 and 59 months after operation. One patient had no neurologic symptoms referable to the carotid artery operated upon, but died of a stroke with symptoms referable to the opposite carotid artery 32 months later.

Neurologic deficits were present in 18 patients at the end of the study. Of the 35 patients who died, three had deficits as a result of original operation, seven had deficits related to lesions of the opposite carotid artery, and one patient suddenly died of a stroke without prior neurologic deficits. There were 68 living patients of whom four had mild deficits, two had moderate deficits, and one was severely incapacitated.

Discussion

The risk of death within 30 days following carotid endarterectomy for symptoms of TIA is very low. There was only one death in this series and in all of the larger series of cases reported, the operative mortality rate has been less than 5%.[2,3,5,10,11,12]

The risk of death within 5 years of operation is significant. Thirty-four per cent of the patients in this series died. It is difficult to compare this mortality rate with other series because of differences in methods of reporting. However, in a controlled and randomized study the mortality rate in a follow-up averaging 42 months was lower in the operated group than the control group.[1] The 34% mortality rate is not unlike that observed in other series of patients with symptomatic atherosclerotic lesions followed for just 5 years. Boyd followed 1,476 patients with intermittent claudication of the lower extremities due to arteriosclerotic occlusive disease.[4] The estimated 5-year mortality rate of patients in the 45–74 year age group was 28%.[4] Serial evaluations were made on 103 patients with autogenous venous bypass grafts performed for atherosclerotic occlusive disease of the femoral and popliteal arteries.[7] The 5-year mortality rate was 26% for patients operated on with symptoms of claudication, 42% if pain at rest was present, and 76% when the indication for operation was gangrene.

TABLE 7. *Cerebrovascular Accident-Opposite Side with Neurological Deficit*

	Mild	Moderate	Severe
Died <5 yrs.	3	2	2
Lived 5 yrs.	2	2	0
Total	5	4	2

The causes of death were remarkably similar in the two groups of patients. Myocardial infarctions were responsible for the death of 24% of patients who had carotid endarterectomies and 26% of the patients who had venous bypass grafts. Other complications of atherosclerosis were responsible for the deaths of an additional 6% of the patients in each group. Five per cent of this group died of strokes.

The mortality rate was influenced by the preoperative status of the patient. Fifty-two per cent of the 70–79 year old group, as compared to the 19% of the 50–59 year old group, died within 5 years. Of the 25 patients with preoperative evidence of arteriosclerotic heart disease 14 (56%) died whereas only 27% of those without angina or electrocardiographic changes died. Six of the eight patients with both arteriosclerotic heart disease and diabetes did not survive 5 years.

Carotid endarterectomy provided permanent relief of preoperative symptoms in 76% of the patients. However, when the preoperative symptoms were of the type classically associated with carotid lesions 84% of the patients were relieved. If the symptoms were nonclassic only 13% were relieved. This failure to significantly effect nonclassic symptoms was previously observed by Fields.[9] This suggests that either the patient's symptoms were not related to the carotid lesion or that carotid endarterectomy cannot improve symptoms related to associated vertebrobasilar insufficiency as effectively as we had hoped.

There is a slight risk of developing permanent neurologic deficit during, or soon after, operation and this incidence has been reported as being between 1 and 7.7%. We observed a 6% incidence in this series but three of the deficits were minor. Transient deficits were observed in another 15 patients. The incidence of all of these early neurologic complications has decreased with experience.[6] Symptoms of stroke which were consistent with the carotid artery operated upon were observed in eight patients of which six occurred at the time of operation and only two occurred during the follow-up period.

The fact that the carotid stenosis operated upon was only part of a generalized process was emphasized by the fact that 11 patients suffered strokes compatible with other lesions of the extracranial cerebral vessels. The additional 17 patients who underwent endarterectomy of the opposite carotid artery within 5 years of original operation reflects the usually widespread nature of atherosclerotic lesions.

Conclusion

The status of 103 patients 5 years following carotid endarterectomies performed for transient cerebral ischemic attacks (TIA) was analyzed.

Thirty-four per cent of the patients died within 5 years. Twenty-four per cent of the patients died of probable myocardial infarctions and an additional 5% died of strokes. Mortality rates were increased when there was preoperative evidence of arteriosclerotic heart disease or diabetes or if the patient was over 70 years of age.

Carotid endarterectomy provided permanent relief of classical carotid occlusion symptoms of contralateral motor or sensory loss, ipsilateral visual disturbances, or dysphasia in 84% of the patients. Symptoms such as dizziness, syncope, headache, seizures, and confusion disappeared in only 13% of patients who were operated upon for only those nonclassic symptoms.

Twelve per cent of the patients had endarterectomy of the opposite carotid artery for appropriate neurologic symptoms and 5% of the patients had prophylactic endarterectomies for asymptomatic lesions.

Sixty-six per cent of the patients were alive at 5 years of whom only three had significant neurologic deficits and four had mild deficits.

References

1. Bauer, Raymond B., Meyer, John S., Fields, William S., Remington, Richard, Macdonald, Mary C. and Callen, Paul: Joint Study of Extracranial Arterial Occlusion: III. Progress Report of Controlled Study of Long-Term Survival In Patients with and without Operation. JAMA, **208**:509, 1969.
2. Blaisdell, William F., Clauss, Roy H., Galbraith, J. Garber, Imparato, Anthony M. and Wylie, Edwin J.: Joint Study of Extracranial Arterial Occlusion: IV. A Review of Surgical Considerations. JAMA, **209**:1889, 1969.
3. Bloodwell, R. D., Hallman, G. L., Keats, A. S. and Cooley, D. A.: Carotid Endarterectomy without a Shunt. Arch. Surg., **96**:644–652, 1968.
4. Boyd, A. M.: The Natural Course of Arteriosclerosis of the Lower Extremities. Proc. Roy. Soc. Med., **55**:591, 1962.
5. DeBakey, Michael E., Crawford, E. Stanley, Cooley, Denton A., Morris, George C., Jr., Garrett, H. Edward and Fields, William S.: Cerebral Arterial Insufficiency: One to 11-Year Results Following Arterial Reconstructive Operation. Ann. Surg., **161**:921, 1965.
6. DeWeese, James A., Rob, Charles G., Satran, Richard, Marsh, David O., Joynt, Robert J., Lipchik, Elliot and Zehl, Donald N.: Endarterectomy for Atherosclerotic Lesions of the Carotid Artery. J. Cardiovasc. Surg., **12**: 299, 1971.
7. DeWeese, James A. and Rob, Charles G.: Autogenous Venous Bypass Grafts Five Years Later. Ann. Surg., **174**: 346, 1971.
8. Eastcott, H. H. G., Pickering, G. W. and Rob, C. G.: Reconstruction of the Internal Carotid Artery. Lancet, **2**:994, 1954.
9. Fields, William S., Maslenikov, Valentina, Meyer, John Stirling, Hass, William K., Remington, Richard D. and Macdonald, Mary: Joint Study of Extracranial Arterial Occlusion: V. Progress Report of Prognosis Following Surgery or Nonsurgical Treatment for Transient Cerebral Ischemic Attacks and Cervical Carotid Artery Lesions. JAMA, **211**:1993, 1970.
10. Rainer, W. Gerald, Guillen, Jorge, Bloomquist, Charles D. and McCrory, Charles B.: Carotid Artery Surgery. Morbidity and Mortality in 257 Operations. Am. J. Surg., **116**:678, 1968.
11. Thompson, Jesse E., Austin, Dale J. and Patman, R. Don: Carotid Endarterectomy for Cerebrovascular Insufficiency: Long-Term Results in 592 Patients Followed up to Thirteen Years. Ann. Surg., **172**:663, 1970.
12. Young, J. R., Humphries, A. W., Beven, E. G. and deWolfe, V. G.: Carotid Endarterectomy without a Shunt. Arch. Surg., **99**:293, 1969.

Discussion

Dr. Jesse E. Thompson (Dallas): As Dr. Rob has shown so nicely, patients with TIAs are ideal candidates for stroke prevention by means of carotid endarterectomy.

Among untreated patients reported in the literature, an average of 35% developed actual strokes if followed up to 5 years and in one study from England, the incidence was 62 per cent.

Our figures are very similar to Dr. Rob's in all respects. In our total series of 537 TIA operations, over a 16-year period, the average mortality was 0.7%. In the last 10 years, since general anesthesia and a temporary inlying shunt have been used routinely, operative mortality in 420 TIA cases has been .5%, which is quite acceptable.

With the routine use of a shunt for cerebral protection, the total incidence of permanent neurologic deficits related to operation has been 1.5% and most deficits are now related to embolization or severe postoperative hypertension.

The long-term functional results have also been satisfactory. 81% of the survivors have had no further TIA while an additional 15% have had fewer attacks of less severity. The total incidence of strokes, including operation induced, long-term, fatal and nonfatal, has been 5%, or a seven-fold reduction in the expected incidence among untreated patients.

Despite these results however, the fourth parameter, long-term survival, so far has shown no statistically significant improvement. The majority of long-term deaths, as Dr. Rob showed, are now cardiac rather than cerebral in origin.

Thus, hypertension and coronary artery disease, especially when associated with previous myocardial infarction, appear to be limiting factors in prognosis and carry a great deal of relevance in the proper selection of patients for operation.

In cerebrovascular insufficiency, however, morbidity is almost as important as mortality and should be emphasized therefore, that the *quality* of survival without a stroke is a very worthwhile and justifiable consideration in these elderly patients with generalized atherosclerotic disease.

DR. GEORGE R. DUNLAP (Worcester): Dr. Rob has been a pioneer in this field. Over the years he has led us down a rather sane and safe path so that we can better care for our patients and I am sure that the public and the profession are in his debt.

Through a fortuitous circumstance, I happened to be in his operating room at St. Mary's Hospital one cold winter morning in 1954, when the first patient with carotid stenosis was being operated upon. At that time, the operation was done under hypothermia and the stenotic lesion was resected with an end-to-end anastomosis.

Hypothermia was induced by piling ice bags on the patient, turning on the electric fans and opening the window. After 2 hours of the cold London weather, the ice bags and the fan, the patient's temperature reached a safe level and the operation proceeded. It was highly successful. This woman who had had many transient ischemic episodes was cured. From that starting point, the rest of us over the years have been better able to help our own patients.

Dr. Rob has talked about the indications for operation and this is an area where we still need his help.

Two years ago, in response to a question as to whether the asymptomatic patient should have a carotid endarterectomy, he indicated that if all took a more careful history, it would be found that more and more patients, in truth, did have symptoms.

But, despite those words of advice, there still are cases where some of us are a little in doubt. For example, what does one do about the patient with bilateral carotid bruit who shows a small cholesterol embolus in the retinal artery on routine examination?

If it is assumed that these patients are tossing off small emboli, either cholesterol or platelet, without other symptoms should they be considered candidates for endarterectomy?

What about the patient who has had a transient stroke recovered, thrombosed one carotid artery and has an asymptomatic stenosis on the other side?

I would like to hear Dr. Rob's thoughts on these two situations.

DR. A. ROBERT CORDELL (Winston-Salem): We remain indebted to Dr. Rob and his colleagues for this important contribution which helps us to answer the difficult question of the role of surgery in occlusive disease of the cerebral vascular system.

It is particularly fitting that continuing work and worthwhile data should come from those who developed this operation.

The group at Bowman-Gray has followed 82 patients for a mean period of 3.8 years after carotid endarterectomies and many of our data corroborates that from Rochester.

At the present time (this study is continuing), 66% remain asymptomatic, 9% had some recurrent transient ischemic episodes, 6.5% had a stroke since the operation, and 23% have died during follow-up, usually of some complication of atherosclerosis.

Operative blood flows on 50 of this 86 patient group are interesting in the overall evaluation of the findings.

In this slide, the blood flow is on the left and these are the intraoperative figures, before and after endarterectomy.

The wide range is interesting in this group which goes from a liter down to as low as less than a hundred milliliters. The mean is in the 350 milliliters per minute range in the common carotid artery. Endarterectomy has relatively little effect in the overall blood flow as measured.

These measurements in this slide are in the external carotid artery and it is interesting that very little change occurred as a result of endarterectomy.

This is the important slide and shows that there has been a mean increase in blood flow in the internal carotid artery as a result of endarterectomy. However, this is probably still not the most important indication for operation in these patients. Prevention of embolization from ulcerated plaque is probably more beneficial. Perhaps a major factor in long-term evaluation is continuing progress of occlusive disease. Such tends to negate benefit from operation.

DR. CHARLES G. ROB (closing): I fully agree with Dr. Cordell that the blood flow is not increased very much with this procedure, but hopefully it prevents micro-emboli which is one of the major factors. I also very much enjoyed Dr. Thompson's comments. He and I have seen eye to eye on this for many years and I would like to thank him for speaking.

It is true that Dr. Dunlop was there when we performed the first operation in London in 1954. I would like to answer his questions first.

First, about the patient with the cholesterol embolus and a carotid bruit, I would operate on that patient because I think one of the main purposes of this operation is to try to prevent micro-emboli.

With regards to the patient with the thrombosis on one side and asymptomatic stenosis on the other, I think our paper answers that question to a certain extent and that is, the high incidence of involvement of the opposite carotid artery in our patients.

I feel that probably one should operate on the other side, if you have a significant stenosis whether it is symptomatic or not.

In conclusion, I would like to mention one thing which was probably just luck—the patient we operated upon in 1954 at that time was aged 66. She is still alive and her doctor wrote to me recently and said "In spite of you, she appears to be indestructible!"

Physiologic Consequences of Positive End-Expiratory Pressure (PEEP) Ventilation

SAMUEL R. POWERS, JR., M.D., RICHARD MANNAL, M.D., MATTHEW NECLERIO, M.S., MARK ENGLISH, B.S., CLIFFORD MARR, B.S., ROBERT LEATHER, M.D., HIDEHIKO UEDA, M.D., GARY WILLIAMS, M.D., WAYNE CUSTEAD, PH.D., ROBERT DUTTON, M.D.

From the Departments of Surgery and Physiology, Albany Medical College of Union University and the Systems Engineering Division, Rensselaer Polytechnic Institute, Troy, New York

THE POST-TRAUMATIC form of the respiratory distress syndrome is characterized by a diminished arterial oxygen tension that is generally unresponsive to increases in inspired oxygen concentration and is associated with an increased shunting of blood through non-ventilated portions of the lung.[1] Improvements in arterial oxygen tension (Pa_{O_2}) will usually occur when the non-ventilated portions of the lung become open to contact with the inspired gas mixture by the use of a mechanical ventilator. Positive end-expiratory pressure (PEEP) will often accomplish this goal as demonstrated by an increase in Functional Residual Capacity (FRC).[12] For this reason, PEEP has been widely advocated for the posttraumatic form of the respiratory distress syndrome.[11] Caution concerning the indiscriminate use of continuous positive airway pressure has been advised since the work of Cournand[4] and others.[9,3,12] Analysis of our preliminary data obtained from 33 severely injured patients including 73 separate alterations in the level of PEEP indicated that in roughly ⅓ of these an increase of PEEP resulted in a worsening rather than an improvement in the calculated shunt. In some patients PEEP produced a reduction in oxygen delivery to the tissues and a fall in tissue oxygen consumption. This report is an analysis of some of the physiologic consequences of increased airway pressure on ventilation, cardiac output and on the peripheral utilization of oxygen. Each individual observation consists of two sequential data profiles at different levels of PEEP. Each profile is made up of nine simultaneously measured and five derived variables.

Methods and Materials

Thirty-three patients were admitted to the Trauma Research Unit of the Albany Medical College with a decreased arterial P_{O_2} which was found to be refractory to an increased inspired oxygen concentration. Twenty-five had suffered acute multiple trauma and eight developed arterial hypoxemia as a complication of a major surgical procedure. Ten patients were over the age of 65 years. At the time of admission to the unit, each patient was intubated with an endotracheal tube, a Swan-Ganz catheter was advanced into the pulmonary artery and a radial artery was cannulated. Urine volume and composition, ECG, EEG and rectal temperature were intermittently monitored in most patients. Respiratory gas flow was measured with a bag-box wedge spirometer assembly which was specially designed for use with a mechanical ventilator.[7] Expired gas was continuously sampled from the endotracheal tube and the concentrations of O_2, CO_2 and N_2 determined by a specially modified mass spectrometer.[8] Airway pressure and in some patients esophageal pressure, was monitored by strain gauge manometers. Cardiac output was measured by the dye dilution technic using cardiogreen dye and a Gilford densitometer. Mixed venous blood was

---

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25–27, 1973.

This work was supported by Grant No. GM 15426 from the National Institute of General Medical Sciences and the General Clinical Research Center, Grant No. 5M01-RR00094m.

obtained from the Swan-Ganz catheter in the pulmonary artery and arterial blood was taken from the indwelling radial artery cannula. In a number of previously studied patients, mixed venous blood was obtained from a central venous catheter. Because of the unrealiability of this sampling site, these data have been excluded. Blood gas analyses were carried out using Po_2, Pco_2 and pH electrodes*. Oxygen content was obtained from standard nomograms. Central venous, pulmonary artery and pulmonary wedge pressures were obtained from the Swan-Ganz catheter and were measured with strain-gauge transducers.

Analog voltages from the wedge spirometer, mass spectrometer and densitometer were transmitted on-line to a medium size digital computer (PDP-15) for analog to digital conversions. Expired quantities of nitrogen and carbon dioxide were computed by integration of the cross product of the expiratory flow signal (wedge spirometer) and gas concentration signal (mass spectrometer). Cardiac output was obtained from the dye curves by a special computer program which estimates the slope of a semilog plot of the exponential portion of the curve by a least squares fit and compares this estimated value with the original data. The printout reports an analysis of variance as a test of the correctness of the derived slope.

Pulmonary shunt fraction was computed off-line using the Berggrens formula with appropriate correction for shift in the oxygen dissociation curve, hemoglobin concentration and dissolved oxygen. (Error of determination 3%) Oxygen delivery was obtained from the product of cardiac output and arterial oxygen content. Tissue oxygen consumption was calculated from the product of the arterial minus venous oxygen difference and the cardiac output.

Pulmonary vascular resistance was calculated whenever possible from the difference between pulmonary artery and pulmonary wedge pressures and the cardiac output. If the pulmonary wedge pressure increased as a result of increased mean airway pressure at a time when cardiac output decreased, it was assumed that the wedge pressure did not estimate left atrial pressure. A rise in true left atrial pressure associated with a fall in cardiac output would be indicative of left ventricular failure, an unlikely occurrence to result from increased airway pressure. Alternatively an increase in alveolar pressure due to PEEP to levels above that in the left atrium will cause the alveolar pressure to be the principal determinant of the pulmonary vascular resistance. It appears that pulmonary wedge pressure will, therefore, accurately reflect changes in pulmonary vascular resistance provided that the catheter is located in an area of the lung which is representative of most of the pulmonary vascular bed.

Results

Patients admitted to the trauma unit showed an average pulmonary shunt of 26% after a 10-minute period of 100% oxygen breathing. The measured (A-a) D O_2 gradient depends on both the shunt fraction and the mixed venous Po_2 and was not in itself an accurate prediction of the degree of shunting. PEEP was utilized in all patients in an attempt to reduce the level of shunt. In 17 of 71 paired determinations the shunt increased, in an additional 24 instances did not result in the expected decrease. The patients were divided into two groups for analysis based on whether the shunt decreased or remained the same (Group I) or increased (Group II) with the addition of PEEP. Each data pair usually represented an increase of 5 cm. H_2O pressure although the increase varied from 0–15 cm. H_2O depending on the severity of the pulmonary lesion and the therapeutic requirements of the patient. The mean value of the shunt was 26% in Group I and 22% in Group II. Cardiac index at the lowest level of PEEP (usually O cm. H_2O) was 4.9 $1/min/M^2$ in Group I and only 3.7 $1/min/M^2$ in Group II. FRC measured at the lowest level of PEEP averaged 1454 ml. and 1563 ml. respectively in Group I and II. Oxygen consumption at the same conditions averaged 158 $ml./min/M^2$ and 165 $ml./min/M^2$. Pulmonary vascular resistance was lower in Group II (95) than Group I (120).

Effects of Increasing PEEP

In a total of 73 paired data sets on 23 patients, the addition of 5–10 cm. H_2O increments of PEEP resulted in a decrease in pulmonary shunt in 54 instances. In 24 such therapeutic interventions there was no change whereas in 17 of the 73 shunt increased. This latter series of 17 pairs of data forms Group II of this study. Any individual patient might appear in both groups as a result of different levels of PEEP or of different times in their clinical course.

Functional Residual Capacity (FRC)

In every case where PEEP resulted in a decrease in shunt (Group I) there was an increase in FRC (Fig. 1); in contrast, the Group II data pairs show a decrease in FRC with the addition of PEEP in seven of 19 sets and a smaller increase in most of the remainder. A significant increase in FRC, 400 ml. or more per 5 cm. increase in PEEP, is the single most important determinant of a decreased pulmonary shunt.

Cardiac Output

PEEP produced a fall in cardiac output in 36 of 70 sets (Fig. 1). There was no significant difference between Groups I and II. No direct attempt was made to improve cardiac output following the addition of PEEP by either inotropic agents or by increasing the fluid load.

---

* IL 313.

Oxygen Consumption

In 15 of 50 data sets in Group I there was a fall in peripheral oxygen consumption even though the shunt improved (Fig. 2). This surprising result was invariably associated with a decrease in cardiac output that more than offset the beneficial effects of the improved shunt. In Group II this fall in oxygen consumption occurred in 12 of 16 situations and in three more no improvement resulted from the addition of PEEP. In almost every instance in which a fall in cardiac output resulted, there was a corresponding fall in oxygen consumption. When cardiac output increased so did oxygen consumption ($r = 0.64$). Oxygen consumption was highly correlated with oxygen delivery (Figs. 3 and 4).

Pulmonary Vascular Resistance

Pulmonary vascular resistance usually but not invariably reflected a change in cardiac output (Fig. 5). Increased airway pressure resulted in an increase of pulmonary vascular resistance in 15 of 22 instances in Group I and in 5 of 14 in Group II. In each instance in which pulmonary vascular resistance changed with increasing PEEP there was an associated change in cardiac output (Fig. 5) ($r = 0.79$).

Pulmonary Wedge Pressure

The change in pulmonary wedge pressure was generally in the same direction as the pulmonary vascular resistance. Increases in pulmonary wedge pressure were usually associated with a fall in cardiac output. This occurred 11 of 12 instances in Group I but was less predictable in Group II. A fall in pulmonary wedge pressure with increasing levels of PEEP was an unusual event (four instances in Group I), but was associated with a rise in cardiac output in three.

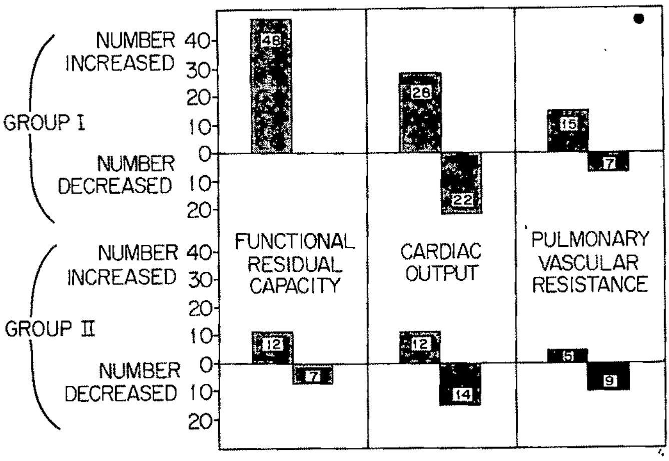


Fig. 1. Numbers of therapeutic interventions which resulted in an increase or a decrease in functional residual capacity, cardiac output and pulmonary vascular resistance. Group I consists of those instances where an increase in PEEP produced a decrease in the shunt fraction, Group II those which resulted in an increased shunt.

Discussion

The application of PEEP to patients suffering from the posttraumatic form of the respiratory distress syndrome may have at least three separate physiologic consequences. These are an increase in the number of ventilated alveoli as evidenced by an increased functional residual capacity, a change in cardiac output and a redistribution of blood flow within the lung from regions that are well ventilated to regions of poorer ventilation. The net effect of PEEP on the oxygen concentration of arterial blood on oxygen delivery to tissues, and ultimately tissue oxygen consumption, is a result of the relative magnitude of each of these effects. An increase in FRC is indicative of a further expansion of already open alveoli as well as to an opening of previously nonventilated alveoli and will be manifested by a fall in the calculated pulmonary shunt and an increase in arterial oxygen concentration.[12] This effect was seen in the majority of patients in this study. Oxygen delivery to the tissues, however, depends on the product of arterial oxygen concentration and the cardiac output. The effect of PEEP on the circulation is, therefore, of equal importance to its effect on ventilation. In one-half of this series, PEEP produced a fall in cardiac output. In approximately one-third of all instances, the observed fall in output out-weighted the improved arterial oxygen content with a consequent decreased oxygen delivery and a fall in tissue oxygen consumption. This phenomenon of decreased cardiac output and oxygen consump-

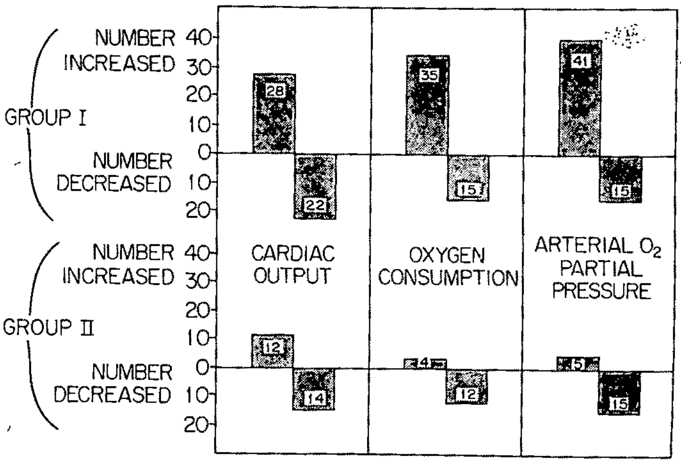


Fig. 2. Numbers of therapeutic interventions which resulted in increases or decreases in cardiac output, oxygen consumption and arterial oxygen tension.

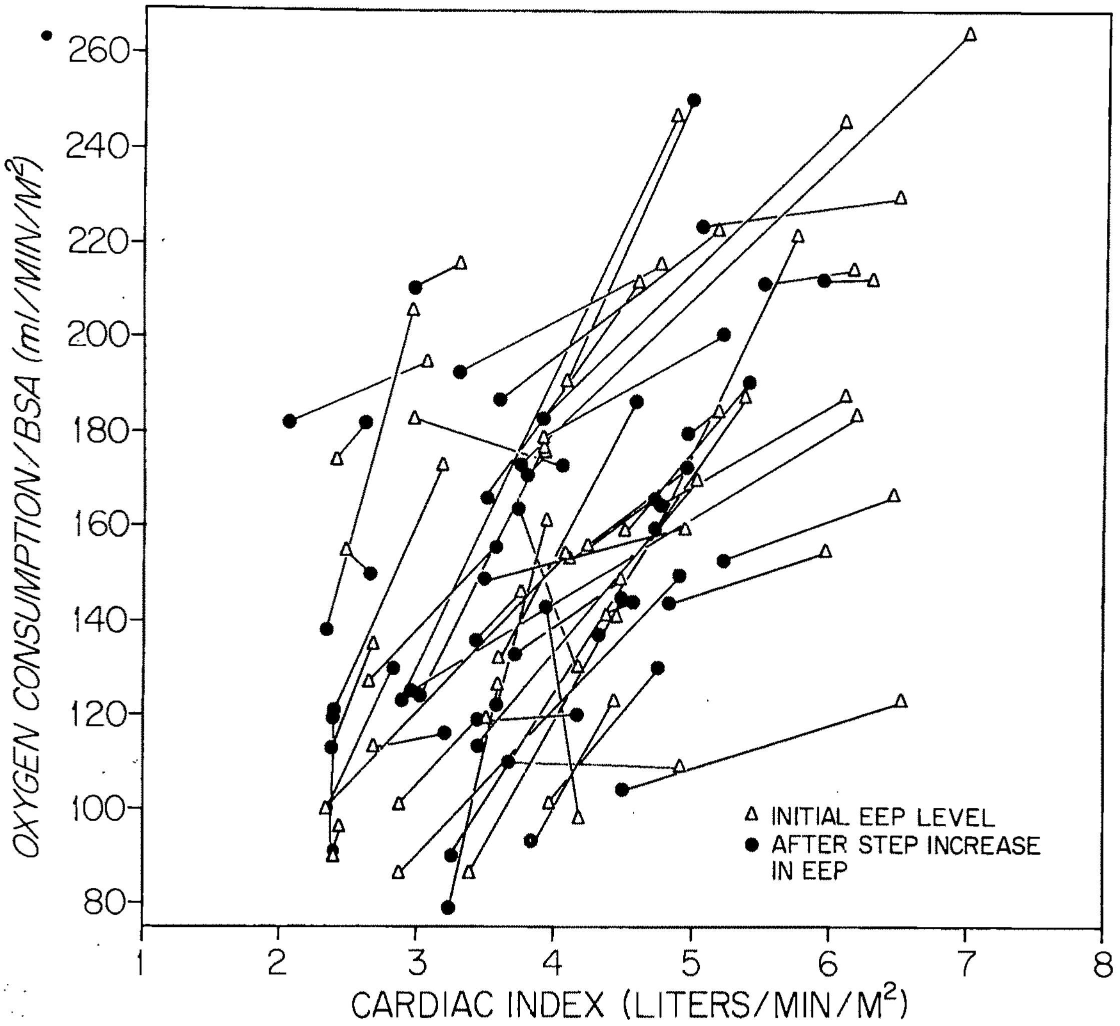


FIG. 3. Absolute changes in oxygen consumption (ml./min/M^2) and cardiac output (L/min/M^2) in response to PEEP. Initial values before the step increase in end-expiratory pressure are shown with open circles. Correlation of the change in oxygen consumption with change in cardiac output yields $r = 0.64$.

tion with the institution of PEEP had been previously noted by Uzawa and Aschbaugh[11] in an animal model of the respiratory distress syndrome. The almost linear relation between cardiac output and tissue oxygen consumption (Fig. 3) was one of the most surprising and most consistent findings of this study. Increases in cardiac output to very high levels was accompanied by an increase in oxygen consumption that never reached a plateau. This observation is consistent with Fales[5] who studied the relationship between oxygen consumption and blood flow in the isolated hind limb of the dog. There was a positive linear correlation with oxygen consumption for all observed values of flow. Our studies suggest that a maximum level of oxygen consumption was never achieved at any level of cardiac output. Some evidence for anaerobic glycolysis would, therefore, be expected at all levels of oxygen consumption with decreasing lactic acid production as flow increases. Gazzaniga[6] has recently studied muscle surface pH, a reflection of anaerobic glycolysis, at various flow rates in the hind limb of dogs. Oxygen consumption calculated from their data revealed a decrease with decreasing flow rates and was accompanied by a fall in muscle pH.

The physiologic mechanism involved in the reduction of cardiac output has been studied in normal animals[9] and normal man[4] and has been ascribed to a decrease in the filling pressure of the right heart. Increased airway pressure will be partially transmitted as an increase in intrathoracic pressure so that the net right ventricular filling pressure (ventricular end diastolic minus intrathoracic) will decrease. There are at least two other mechanisms which may alter cardiac output as a consequence of increased PEEP. Improved arterial oxygen content as a result of PEEP may increase the peripheral resistance and decrease the rate of venous return to the right heart. PEEP increases pulmonary vascular resistance by a direct compressive effect on the pulmonary capillaries. Evidence for all three mechanisms occurred in this series with the most important being the effect on pulmonary vascular resistance (Fig. 5). The levels of PEEP used in these patients (maximum 10 cm. H_2O) rarely if ever approached the pressure which Cournand[4] found to be associated with a significant fall in stroke

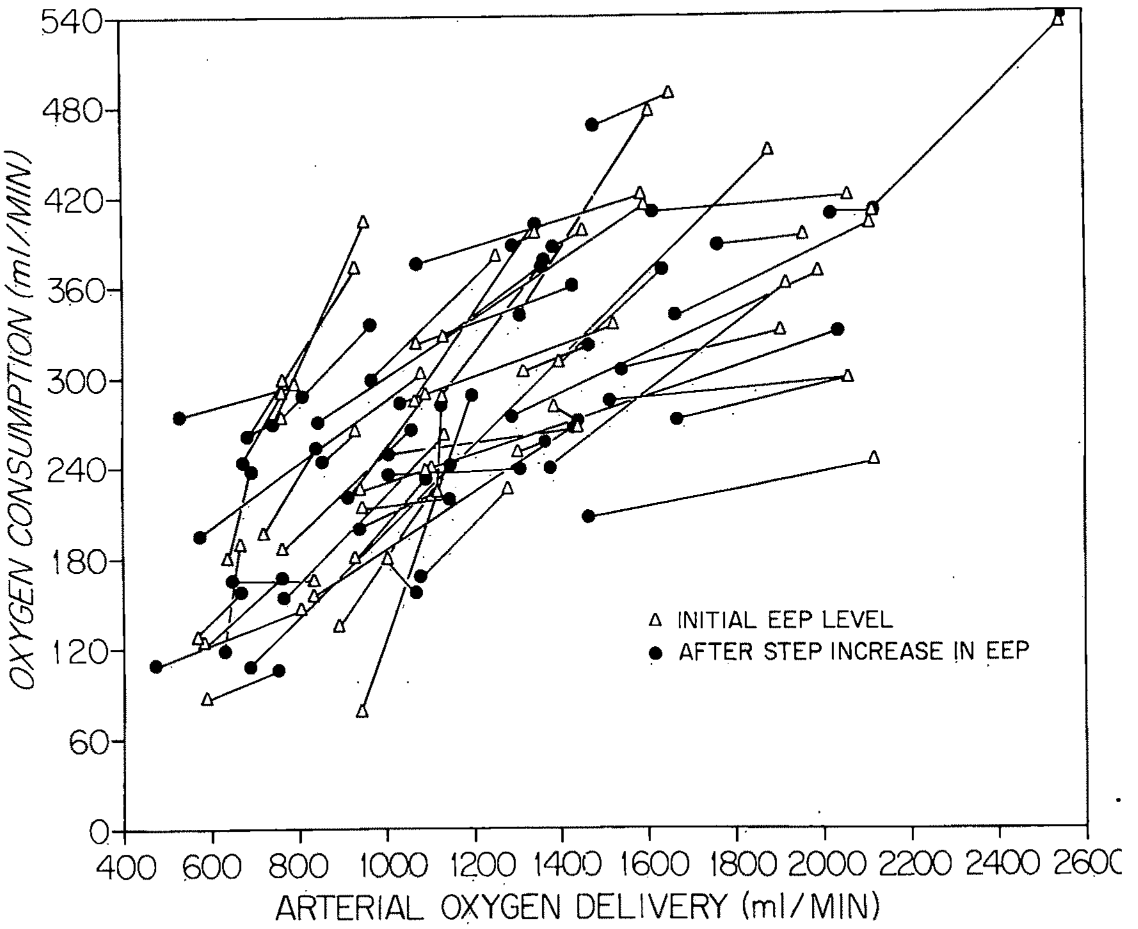


FIG. 4. Absolute changes in oxygen delivery (cardiac output x arterial oxygen content) in response to PEEP (r approaches 1.0).

volume (15–20 cm. H_2O). Decreased pulmonary compliance in patients with respiratory distress syndrome would limit the effect of PEEP on intrathoracic pressure to less than one-half of its absolute value, a change in amount which by itself could not account for the observed fall in cardiac output. On the other hand, the calculated pulmonary vascular resistance was increased in 20 of 36 instances when the cardiac output fell (Fig. 5).

The deleterious effects of PEEP on cardiac output in our patients was, therefore, due to the additive effect of the increased pulmonary vascular resistance and limited or slightly decreased filling pressure of the right ventricle (Fig. 6). In the normal individual, an increase in pulmonary vascular resistance produces a rise in filling pressure and consequent increase in stroke volume. Any increase in intrathoracic pressure which results from PEEP will tend to reduce right ventricular filling pressure at the time when an increase is necessary to preserve stroke volume. Caldini[3] has shown that with rapid fluid infusion into the right side of the heart the cardiac output can be increased to very high levels in the face of increased pulmonary vascular resistance. It is probable that the reduced cardiac output seen in almost half the patients of this study could have been avoided in at least some cases by more vigorous intravenous fluid therapy. Another possible mechanism for decreased left ventricular stroke volume is an increased transmural pressure across the ventricular wall. This might result from the increase in intrathoracic pressure and could decrease coronary blood flow especially in older patients with coronary artery disease.[2] In this regard 13 of 19 patients over the age of 55 showed a fall in cardiac output with the addition of PEEP.

An increase in cardiac output was seen in some patients of both groups following the application of PEEP and was generally associated with a decrease in shunt. Improvement in alveolar P_{O_2} in the poorly ventilated alveoli as evidenced by a decrease in shunt would be associated with a fall in vascular resistance to these areas. Lopez-Majano[10] has demonstrated that regional alveolar hypoxia results in a decrease in regional pulmonary blood flow in man. This effect is due to a local increase in pulmonary vascular resistance. Conversely, an improvement in alveolar P_{O_2} of these areas as a result of PEEP would lead to a net reduction in pulmonary vascular resistance and a consequent increase in cardiac output. It is of interest that a fall in pulmonary vascular resistance would result from improved ventilation of poorly ventilated regions (virtual shunt) as well as from reopening of completely non-ventilated alveoli (true shunt). Table

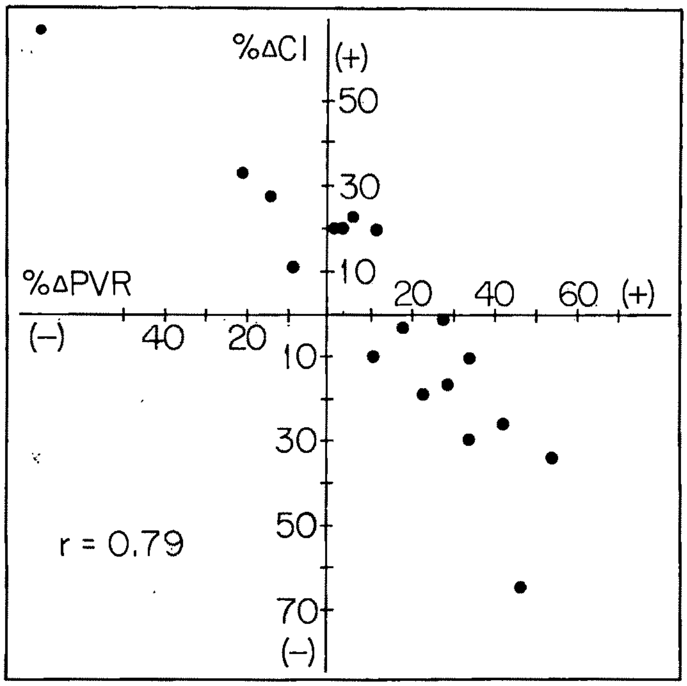


FIG. 5. Relation of the per cent change in cardiac index to the per cent change in pulmonary vascular resistance following a change in PEEP (r — 0.79).

1 illustrates the data from such a patient. Our hemodynamic studies in the patients of this series were not carried out during the period of 100% oxygen breathing which was used for the shunt calculation. It is probable that those patients in Group II who demonstrated a fall in vascular resistance with PEEP would have fallen into Group I if the effect of PEEP on the shunt had been observed at the same inspired Po_2 as were used for the hemodynamic studies.

Regional pulmonary vasoconstriction will occur in regions of alveolar collapse and will tend to divert blood away from the collapsed alveolar unit and through the better ventilated portions of the lung. This is a normal compensatory mechanism that acts to minimize the effect of the decreased FRC and collapsed alveoli. PEEP on the other hand will obstruct precisely those capillaries which flow past ventilated units since the positive pressure will be predominantly transmitted to open alveoli. The net effect of PEEP may, therefore, be to override the natural compensatory mechanism and direct pulmonary blood flow passed collapsed or non-ventilated portions of the lung (Group II). PEEP can have a beneficial effect on pulmonary shunting only if non-ventilated alveoli are recruited as evidence by an increase in FRC.

TABLE 1. *Virtual shunt obtained during a period of 20% oxygen breathing and true shunt obtained after 10 minutes of 100% oxygen breathing at two levels of PEEP. Virtual shunt improves with increased PEEP whereas true shunt does not.*

	PEEP = 5cmH$_2$0		
Time	Washout Gas Composition	FRC (ml)	Shunt (%)
1415	20% 0_2–80% Argon	2451	22.7
1435	100% 0_2	1611	13.6
	PEEP = 10cmH$_2$0		
Time	Washout Gas Composition	FRC (ml)	Shunt (%)
1550	20% 0_2–80% Argon	2413	11.4
1610	100% 0_2	1070	15.3

These studies suggest that a significant physiologic parameter in the management of the severely injured patient is the peripheral oxygen consumption. Shunt fraction and cardiac output frequently, but not invariably reflected improvement in tissue oxygenation. Increases in the quantity of oxygen delivered to the tissue, however, resulted in increased oxygen utilization. Cardiac outputs in the range of more than twice normal with high oxygen saturations was incapable of satisfying the oxygen demands of these patients. The optimum level of oxygen consumption in the severely injured patient has not been determined but the very high cardiac indices seen in these series is apparently a biologic response to an increased oxygen demand. A continuous rise in oxygen consumption which paralleled the rise in oxygen delivery is at variance with the concept of a block in cellular oxygen transport or utilization. The peripheral tissues are apparently able to utilize the increased quantity of oxygen which is provided by the high cardiac output.

PEEP is a therapeutic intervention which has the potential for increasing oxygen delivery in patients with

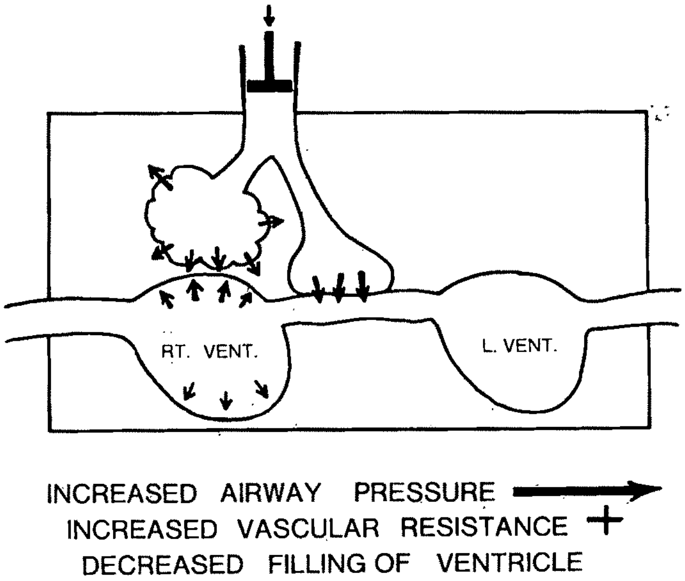

RT. VENT.
L. VENT.
INCREASED AIRWAY PRESSURE →
INCREASED VASCULAR RESISTANCE +
DECREASED FILLING OF VENTRICLE

FIG. 6. Physiologic mechanisms for the decrease in cardiac output seen in approximately one-half of the therapeutic interventions with PEEP. Increased alveolar pressure increases pulmonary vascular resistance while increases in intrathoracic pressure limit the filling of the right ventricle. The effects are additive.

increased pulmonary shunting. This was accomplished in most of the patients of this series (Group I) by increasing the oxygen content of arterial blood following a decrease in the magnitude of the shunt and in addition, in some patients, by increasing cardiac output. Both the decreased shunt and the decreased pulmonary vascular resistance occurred as a result of an increase in FRC. On the other hand, in some patients the improved shunt was more than offset by the fall in cardiac output with a consequent reduction in oxygen delivery and consumption.

A small group of patients (Group II) demonstrated an increased shunt in response to PEEP and in a majority of these an associated fall in oxygen delivery and consumption. The effect of PEEP in this group of therapeutic interventions was probably detrimental to the patients clinical course.

Ideal management should produce an increased oxygen consumption. This generally occurred when the application of PEEP resulted in a fall in the shunt fraction without a significant rise (more than 2 cm. H_2O) in pulmonary wedge pressure. On the other hand, an increase in shunt fraction especially when associated with a fall in arterial Po_2 was indicative that not only had blood been driven past poorly ventilated alveoli but that a fall in cardiac output had likely occurred. This sequence was an indication for the immediate reduction in the level of PEEP.

Summary

1) Mechanical ventilation with PEEP may affect favorably the pulmonary shunt fraction by opening collapsed alveolar units. This can be demonstrated by an increase in FRC. In some patients, PEEP may cause a worsening of the shunt fraction by shifting the distribution of pulmonary blood flow toward non-ventilated regions of the lung.

2) PEEP may result in an increase or a decrease in cardiac output due primarily to its effect on pulmonary vascular resistance.

3) Ideal ventilatory therapy is demonstrated by an increase in tissue oxygen consumption.

4) Management of these difficult patients is most easily accomplished when facilities for the measurement of FRC, cardiac output, pulmonary vascular resistance as well as blood gases are available.

5) The measurement of pulmonary wedge pressure in addition to the shunt fraction provides a usually reliable guide to the altered pattern of pulmonary hemodynamics which may occur with the use of PEEP. These combined measurements will help to define the level of PEEP that will adversely effect the clinical course of the patient.

References

1. Ashbaugh, D. G., Bigelow, D. E., Petty, T. L. and Levine, B. E.: Acute Respiratory Distress in Adults. Lancet, 2:319, 1967.
2. Buckberg, G. D., Fixler, D. E., Archie, J. P. and Hoffman, J. I. E.: Experimental Subendocardial Ischemia in Dogs with Normal Coronary Arteries. Circ. Res., 30:67, 1972.
3. Caldini, P.: Pulmonary Hemodynamics and Arterial Oxygen Saturation in Pulmonary Embolism. J. Appl. Physiol., 20: 1965, 184.
4. Cournand, A., Motley, H. L., Werko, L. and Richards, D. W.: Physiological Studies of the Effects of Intermittent Positive Pressure Breathing on Cardiac Output in Man. Am. J. Physiol., 152:162, 1948.
5. Fales, J. T., Heisey, S. R. and Zierler, K. L.: Dependency of Oxygen Consumption of Skeletal Muscle on Number of Stimuli During Work in the Dog. Am. J. Physiol., 198: 1333, 1960.
6. Gazzaviga, A. B., Byrd, C. C., Stewart, D. R. and Gross, R. E.: Effects of Dexamethasone and Chlorpromazine on Skeletal Muscle Surface Hydrogen Ion Concentration during Cardio-Pulmonary Bypass. Ann. Surg., 176:757, 1972.
7. Gisser, D., Newell, J. and Powers, S. R.: A Refined Bag-box Spirometer. JAAMI, 6:167, 1972.
8. Kavner, D., Dizio, S. and Powers, S. R.: A New Method for Measuring Blood Gas Partial Pressure and Content. Advances in Chemistry: American Chemical Soc. In Press.
9. Lenfant, C. and Howell, B. J.: Cardiovascular Adjustments in Dogs during Continuous Pressure Breathing. J. Appl. Physiol., 15:425, 1960.
10. Lopez-Majano, V., Wagner, H. N., Twining, A. B., Tow, D. E. and Chernick, V.: Effect of Regional Hypoxia on the Distribution of Pulmonary Blood Flow in Man. Circ. Res., 28, 550, 1966.
11. Uzawa, T. and Ashbaugh, D. G.: Continuous Positive-Pressure Breathing in Acute Hemorrhagic Pulmonary Edema. J. Appl. Physiol., 26:427, 1969.
12. Powers, S. R., Burdge, R., Leather, R., Monaco, V., Newell, J., Sardar, S. and Smith, E. J.: Studies of Pulmonary Insufficiency in Nonthoracic Trauma. J. Trauma, 12:1, 1972.
13. Sarnoff, S. J., Maloney, J. V. and Wittenberger, J. L.: Effect on the Circulation of Electrophrenic Respiration and Positive Pressure Breathing during the Respiratory Paralysis of High Spinal Anesthesia. Ann. Surg., 132:923, 1950.

Discussion

Dr. Thomas F. Nealon, Jr. (New York City): This is a very worthwhile adjunct to the treatment of ventilator patients who require adequate ventilation and more important—adequate oxygenation. Dr. Powers' suggestion that the measure of wedge pressures may help to determine in which instances this procedure will be beneficial, is certainly a worthwhile clinical adjunct that we might now use.

Since this is such a beautiful physiologic study, I would like to bring up one clinical problem that we have encountered with this particular technic.

We have been concerned with the large numbers of pneumothoraces seen at our hospital. Dr. Steier in our department has found there was a precipitous increase in number of these occurrences in the patients who were being ventilated. We found that there was only a quarter per cent incidence in those patients who were ventilated with pressure ventilators, which increased to 7% when volume ventilators were used and it increased to 17% when PEEP was included.

As a matter of fact, at the thoracic meeting last week, there were several reports in which the incidence of pneumothorax with PEEP ran as high as 20%. This should not discourage the use of this procedure because it is extremely valuable and possibly the only technic to use in those patients when there is difficulty in providing adequate oxygenation.

Conversely, I think it is very important to be aware of this catastrophic event and unless it is recognized immediately, and decompressed, pneumothorax can be a fatal complication.

However, it certainly should not discourage the use of this very valuable technic.

Dr. George H. A. Clowes, Jr. (Boston): Sam Powers, in my opinion, has done a tremendous thing for us in his work during the past few years in clarifying the physiological effects of respiratory dysfunction and the use of respirators as applied to man. I think we all owe him a debt for coming up with the kind of data he showed this morning.

Another point which should be mentioned is that perhaps the way to avoid having to use PEEP is to start using a respirator earlier in the patient's course. I have become very much impressed with the reduction in respiratory problems that we have had with septic, injured, post-shock patients, simply by following the rule that, if on breathing air a patient's arterial blood oxygen tension is less than 65 mm. Hg, we will intubate him, start him on a respirator and regulate the blood gases. Later the question is asked as to why he has respiratory trouble. It is my impression that we have nearly halved the number of serious shunt problems on our general surgical service.

I would like to consider with you one other problem. Sam Powers has shown us that we may reduce the cardiac output seriously by the injudicious use of PEEP. We might ask the question why does the patient have a high cardiac output in the first place? Well, it is partly because he may be pumping poorly oxygenated blood, but more importantly it is because people who are in the post-injury state or who are seriously septic have a low peripheral vascular resistance probably due to peripheral metabolic disorders. If they are to do well, they must have a high cardiac output.

What is the effect of lowering this cardiac output by PEEP or other mechanisms? First of all, the venous oxygen tension is reduced and this in turn makes the shunt situation appear much worse, as Dr. Powers has shown by his calculations. In other words, the oxygen tension in the arterial blood is immediately lowered.

The second thing is that a low cardiac output in the seriously septic or post-traumatic patient probably changes his peripheral metabolism from one of glucose utilization to one of fat utilization. Experimentally the oxygen appears to be consumed primarily by fat oxidation. Although glucose continues to be taken up by muscle much more lactic acid is produced from it, and in turn, the tendency to acidosis becomes much worse.

So all things considered, it seems to me that the fellow who uses PEEP must follow the arterial and venous oxygen tensions as well as the degree of metabolic acidosis that are present in order to regulate the respiratory and circulatory support accordingly.

Dr. Samuel R. Powers (Closing): First is the question of pneumothorax. There appears to be an enormous variation in the incidence of this complication in the various institutions which routinely use positive end-expiratory pressure.

It has been a relatvely rare occurrence in our unit and we believe this has to do with the form of the inflation pressure pulse rather than its magnitude.

If the respirator delivers very short inspiratory phase then a high peak pressure will result, whereas one can deliver the same quantity of gas with a more prolonged inspiratory phase. End-expiratory pressure can be used without developing a high peak pressure. It is our impression that most of the new volume cycled respirators allow this change in pattern of ventilation.

It is essential that pneumothorax be recognized immediately and for this reason we never permit a patient who is having positive end-expiratory pressure to be alone in the room. A nurse or a physician is there every 60 seconds of every 24 hours a day. If this is recognized and a chest tube is put in place, there is no reason to discontinue the same level of positive end-expiratory pressure.

I particularly appreciate Dr. Clowes' comments. I am sure that most of you realize that Dr. Clowes is the pioneer who presented the original report on the very high cardiac outputs in patients in the post-injury state. We agree that the early use of the respirator is most important. Our house staff has become so expert and does these things so early that we now have difficulty getting patients to study. They are well managed when they are first seen.

One other point. Our data suggest that oxygen delivery is the factor which determines oxygen consumption. The most important determinate of oxygen delivery is the hemoglobin level. It makes little sense to try and increase the Po_2 of a patient a few millimeters with a potentially dangerous modality when oxygen delivery can be increased by much greater amounts by the simple addition of a blood transfusion.

Hiatus Hernia:

(A 20-year Retrospective Survey)

P. R. ALLISON

From the Department of Surgery, The Radcliffe Infirmary, Oxford, England

THE AMERICAN SURGICAL ASSOCIATION has continually shown me great kindness, courtesy and hospitality, but on two occasions it has bestowed upon me exceptional privileges; the first was granted 20 years ago when I was given honorary membership, the second is this opportunity of giving an account of my stewardship.

My account relates to the study of 898 patients with hiatal hernia and the observations are limited to a 20-year period to 1970. During this time, my associates and I have used an operative technic described in *Surgery, Gynecology and Obstetrics* in 1951.[1] I shall refer to this procedure as the standard operation, meaning by that only that its use has been standard for us.

Such adherence to a particular operative treatment may expose us to accusations of obstinacy, but at least we have collected some reliable information which would have been denied to us if we had pursued each new modification or change of treatment as it came along.

The necessity of condensing this 20-year review into this brief report has not been easy and it is only possible to present the dry ashes after the cremation.

Of the 898 patients, 537 were females and 361 were males, giving a ratio of 3:2 in favor of females, Table 1.

If we accept that some sliding herniae have a paraesophageal pouch and many paraesophageal herniae have a sliding element, we can group them into predominantly sliding and predominantly paraesophageal herniae. There were 95 paraesophageal (77 female and 18 male), and 801 sliding herniae (460 female to 341 male). Paraesophageal hernia, therefore, is comparatively uncommon and represents 10.6% of the total in this series. For paraesophageal hernia the ratio of female to male is 4 to 1, whereas for sliding hernia the female to male ratio is 1.3 to 1.

The relationship between symptoms and many factors was studied, but of these it is possible to mention only weight and emotional disturbances. In paraesophageal hernia there was no convincing relationship of symptoms to weight but in sliding hernia there was a positive relationship in 67.8% of males and 53.6% of females. The effect of emotional disturbances, anxiety, domestic and business tensions is notoriously difficult to assess because the patients themselves are not always aware of them. The simple results of direct questioning suggested that in paraesophageal hernia there was a positive relation in 30% of both men and women, while in sliding hernia the corresponding figures were 23% of males and 34% of females. These low figures were a little unexpected. Impressions over the years would have put the figures more in the region of 75%.

The commonest symptoms were pain, flatulence, regurgitation, and vomiting, dysphagia, overt bleeding and anemia. Others such as dyspnea and hiccup were less common. A detailed analysis of all these symptoms must await a further publication, but it is worth stressing at this stage that more than half of the patients with paraesophageal hernia complained of regurgitation, and in those patients with sliding hernia who complained of dysphagia about an equal number had stenosis as had only superficial esophagitis.

Other associated organic abnormalities were very common, especially arterial disease and hypertension. Sliding herniae were accompanied by pyloric and duodenal pathologic changes (including diverticula) in 16%, by gastric disease (excluding gastritis) in 5.4% and by gallbladder disease in 22.6%. A lower esophagus lined by gastric mucosa was present in 9.3% (Table 2).

In patients with sliding hernia reflux from the stomach to the esophagus was demonstrated radiologically in 68.3% but the hernia was diagnosed by esophagoscopy in 88.1%.

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25–27, 1973.

TABLE 1. *Sex Analysis of 898 Patients with Diaphragmatic Hiatal Hernia*

	Males	Females	Total
Paraoesophageal	18	77	95
Sliding	341	460	801
Not Stated	2		2
Total	361	537	898

A comprehensive classification of macroscopic esophagitis has been described elsewhere,[2] but for present purposes the degree of esophagitis has been classified into six categories; the first three are superficial, category four is stenosis by edema, five and six are associated with fibrous stricture. The details of incidence are shown in Table 3, but very roughly about 25% had no esophagitis, 50% had superficial esophagitis and 25% showed narrowing of the lumen.

Of the 898 patients all had some degree of medical treatment, 553 had surgical treatment and 345 relied entirely on medical treatment (Table 4). The operations performed are shown in Table 5.

Only the results of standard reduction with or without drainage gastrostomy are considered here. There were 374 of these procedures, and for reasons that will become apparent they have been divided into those performed by the author (Group A 153) and those performed by associates (Group B 221). In Group A there were no deaths and in Group B there was one death from pulmonary embolus, giving an overall mortality rate of 0.3%.

There was some form of immediate complication in 31% of the patients. Respiratory infections, wound infections, and deep vein thrombosis accounted for most of the complications. Late complications included wound pain and incisional hernia, and ankle swelling when the legs were left dependent. These amounted to 21% of the total.

TABLE 2. *The Association of Hiatal Hernia with other Organic Abnormalities*

	Paraesophageal Hernia	Sliding Hernia
Spinal Deformity	18%	12.7%
Respiratory Disease	22%	17.4%
Collagen Disease	0	2%
Pyloric & Duodenal Disease (Including Diverticula)	8.4%	16%
Gastric Disease (excluding gastritis)	12.6%	5.4%
Gall Bladder Disease	27.6%	22.6%

Colon Disease—Not Significant Because of the Absence of Routine Radiological Studies

	Paraesophageal Hernia	Sliding Hernia
Gastric-lined Esophagus	4.3%	9.3%
Esophageal Diverticula	3.2%	2.8%
Crico-pharyngeal Disorders	0	0.9%
Others (cardio-vascular disease, etc.)	53.8%	52%

TABLE 3. *Degree of Esophagitis in Sliding Hernia*

	Males	Females
No Esophagitis	23.4%	21.5%
Superficial Esophagitis (Grades 1, 2 & 3)	50.7%	55.8%
GRADE 4 (Stenosis by edema)	5.9%	7.0%
Fibrous Stricture (Grades 5 & 6)	20%	15.7%

Any discomfort in the chest or upper abdomen was included as wound pain. Such discomfort could persist from 6 to 10 months, was subject to climatic changes and only in occasional patients lasted 2 to 3 years.

The immediate effects of operation were good and competent cardiac function was restored in 90.4% of those who had a radiological check before leaving hospital.

Preoperative pain and discomfort was completely relieved in 82% of patients with sliding hernia, improved in 5%, unchanged in 8%, made worse in 0.4% and not recorded in 4.6%. Flatulence was completely relieved in 71%, improved in 16%, unchanged in 12% and worse in 1%.

Regurgitation was completely relieved in 81%, improved in 9%, unchanged in 9%, worse in 0.2% and unrecorded in 0.8%.

Dysphagia was completely relieved in 70%, improved in 14%, unchanged in 11%, worse in 3% and unrecorded in 2% (Table 6). Those made worse were only temporarily so and this condition was caused by too tight repair of the hiatus. These results were elicited from the total number of patients with sliding hernia and were almost identical if subdivided into Groups A and B.

Of the 553 patients treated surgically, 421 were alive at the time of the survey, 118 were dead and the condition of 14 was unknown. When the patients were reviewed radiologically, the presence of a stomachal pouch above the diaphragm, no matter how small, or the presence of reflux from stomach to esophagus, tested in exactly the same way as before operation, were taken to indicate recurrence. By these rigid standards, radiological recurrence was found in 33% of paraesophageal hernia and in 49% of sliding hernia.

TABLE 4. *Treatment of 898 Patients with Hiatal Hernia*

Medical Treatment only Including Esophagoscopy	Surgical Treatment
345	553

TABLE 5. *Type of Operation Performed in 553 Patients*

1.	Standard reduction	332
2.	Standard reduction + gastrostomy	42
3.	Standard reduction + vagotomy and drainage	21
4.	Standard reduction + cholecystectomy	14
5.	Standard reduction + cholecystectomy and gastrostomy	8
6.	Standard reduction + cholecystectomy and vagotomy and drainage	1
7.	"Modified" reduction	5
13.	Reduction + other complex operations, e.g. Heller's, etc.	39
14.	Other operations, e.g. Leigh Collis	24
15.	Resection	67

There are some important aspects of this high recurrence rate: 1) it was the same in groups A and B, so that it is a reflection on the operation and the kind of patient rather than on the experience of the individual operator; 2) the recurrences increased steadily with the years after operation—thus in group A there were 27 recurrences in the first year, 28 between 1 and 5 years, 15 between 5 and 10 years and 11 after 10 years. Very similar figures were found in group B. There is, therefore, no suggestion that if cardiac function remains competent for 5 years the patient can be considered cured. This underlines the necessity for comparison with the results of other operations observed over a correspondingly long period of time. It was noted at the time of survey that many patients, immediately freed from symptoms, had grossly overeaten and become obese, despite strict warnings to the contrary.

The third point to be made about the radiological recurrences is that by no means did all the patients have any recurrence of symptoms. Of the 374 operated upon, 43 patients were completely freed of all symptoms but were found to have radiological recurrence, and of 284 who had return of some symptom in some degree, 86 showed that cardiac function was competent. These findings must be assessed with due regard to the existence of other causes of flatulent dyspepsia. Of those who had return of symptoms, the great majority volunteered that they were mild and not to be compared with their discomfort before operation, but this statement must be interpreted in the light of other factors such as the diminution of the severity of discomfort with advancing years, the anxiety of patients to please those who have looked after them, and the philosophy of those who "learn to live with their troubles".

TABLE 6. *Immediate Effects of Operation for Symptoms of Hiatal Hernia*

	Complete Relief	Improvement	Unchanged	Worse	Unrecorded
Pain	82%	5%	8%	0.4%	4.6%
Flatulence	71%	16%	12%	1%	0%
Regurgitation	81%	9%	9%	0.2%	.8%
Dysphagia	70%	14%	11%	3%	2%

References

1. Allison, P. R.: Surg. Gynecol. Obstet., 92:419, 1951.
2. Allison, P. R.: Scand. J. Thorac. Cardiovasc. Surg., 6:318, 1972.

DISCUSSION

DR. LUCIUS D. HILL (Seattle): When Professor Allison discussed our paper at the 1970 meeting, he prefaced his remarks by saying that whatever he had to say was steeped in prejudice.

Few men demonstrate the stature to be so forthright. Today, he has presented an objective assessment of his procedure without prejudice. I hope my remarks can be as objective as his.

For an operation to be of value, it must attack the underlying derangement with an acceptable degree of success and should be reproducible in other hands.

The basic derangement that Professor Allison alluded to in hiatal hernia and gastroesophageal reflux is an inadequate lower esophageal sphincter pressure which allows reflux. This is in addition to the herniated viscus.

The sophisticated gastroenterologist, in this country at least, is asking the surgeon whether he can indeed correct the lower esophageal sphincter pressure and thereby offset reflux.

He is asking more of the surgeon than simply can he produce a nice postoperative radiogram which the radiologist states shows no recurrent hernia.

Until we can present hard data demonstrating that we are able to improve the lower esophageal sphincter pressure, faith in our operative manipulations among sophisticated gastroenterologists will not improve.

Undoubtedly we are not performing the Allison procedure as he depicted in this country. We are certainly not performing it as well as he does.

The most recent analysis of the effect of the procedure in terms of reflux is measured by pH and pressure determinations by Woodward and his group as you know, indicated a 54% persistent reflux and 39% anatomical recurrence in 127 patients. Other institutions throughout the country reported a similar experience.

An analysis of 80 patients having median artery repair, studied by pre- and postoperative pH and pressure studies at our institution, shows a mean increase of 6.97 mm. Hg in the postoperative sphincter pressure as opposed to the preoperative sphincter pressure.

In three of these patients, the sphincter pressure was unimproved. In these three patients the results were not as good as those in whom the LESP was improved indicating a high degree of correlation between improvement and symptoms and improvement in sphincter pressure.

Median arcuate posterior repairs have now been followed for 13 years. The question arises are these results reproducible?

Other centers, as far away as Santiago, Chile, utilizing this procedure, have had a low recurrence and a high degree of correction of reflux.

The most significant recent report is that of Thomas and Hall at the University of California Medical Center in San Francisco. These authors reporting before the Pacific Coast Surgical Association on a series of 79 patients operated upon over a 6½ year period with no anatomical recurrence and a correction of reflux as measured by pH and sphincter pressure studies in 93% of patients.

It is noteworthy that these patients were treated at the V.A. hospital in San Francisco. Forty two of them were confirmed alcoholics and 15 patients were under psychiatric care for serious mental derangement. If one can produce these results in that group of patients, the operation can indeed be said to have stood the acid test. I am certain that few centers in this country are performing the Allison technic as Professor Allison himself does it. I suspect if we could make the trip to Oxford and observe Professor Allison first-hand, that we too could come up with a high degree of reproducibility.

Dr. Conrad Lam (Detroit): It has been a pleasure to hear Philip Allison tell us of the additional experience he has had over the past 20 years with his repair of hiatus hernia. It was just 20 years ago preceding the meeting of this Association in this city, that Dr. Leo Kenney and I presented a paper before the American Association for Thoracic Surgery entitled "The Problem of the Hiatus Hernia of the Diaphragm". We proposed that the problem would largely be solved by the routine use of a standard anatomic repair, the Allison repair.

During the succeeding two decades and after an experience of more than 500 more operations, we have had no valid reason to change the technic, although some distinguished colleagues have proposed different operations. The previous discussant, Dr. Hill, has suggested that the defect be approached through an abdominal incision and that the stomach be sutured to the arcuate ligament. Others have advised us to wrap the stomach around the lower part of the esophagus to prevent reflux. One of these operations bears the name of one of Michigan's fine motor cars—the Mark IV!

I show one of the slides we used 20 years ago to illustrate the beauty of the Allison operation, appropriately done in Hollywood Technicolor! The next four slides illustrate a problem we encountered a year ago. This film, made 7 years ago, shows a hiatus hernia in a 55-year-old woman living in a neighboring city. A thoracic surgeon was consulted, but he refused to do an operation until she had lost some weight. This she could not or would not do, and she suffered for 6 more years. The second film was made a year ago, and it appears that we might be dealing with a shortened esophagus. This proved to be true. For awhile at the operation, it looked like it would be impossible to get the esophago-gastric junction down to the level of the diaphragm and my assistants suggested that fundoplication would have to be done. Of course, this would have meant that we would still have stomach up in the chest. But with mobilization of the esophagus up to the arch of the aorta, we were finally able to get the esophago-gastric junction down to the diaphragm.

A month later, she was unable to swallow liquids and a film of the esophagus showed near complete obstruction at the lower end of the esophagus. At this point, I began to think about such things as resection of the strictured area, but a single dilatation with the Hurst dilator produced the excellent result shown in the final slide.

This patient and her surgeon are grateful to Philip Anderson for this contribution to the surgery of hiatal hernia.

Professor Philip R. Allison (Closing): I was particularly interested in the remarks Dr. Hill made about pH and pressure measurements. I am sure these are all important things for investigation of future cases.

I would also like to say what a great relief to me and how pleasant it was to hear him say in his last sentence that if he came to Oxford he would be able to produce such a high degree of reproducibility instead of a high degree of recurrence!

The Weavenit® vascular prosthesis. An ideal porosity for better healing.

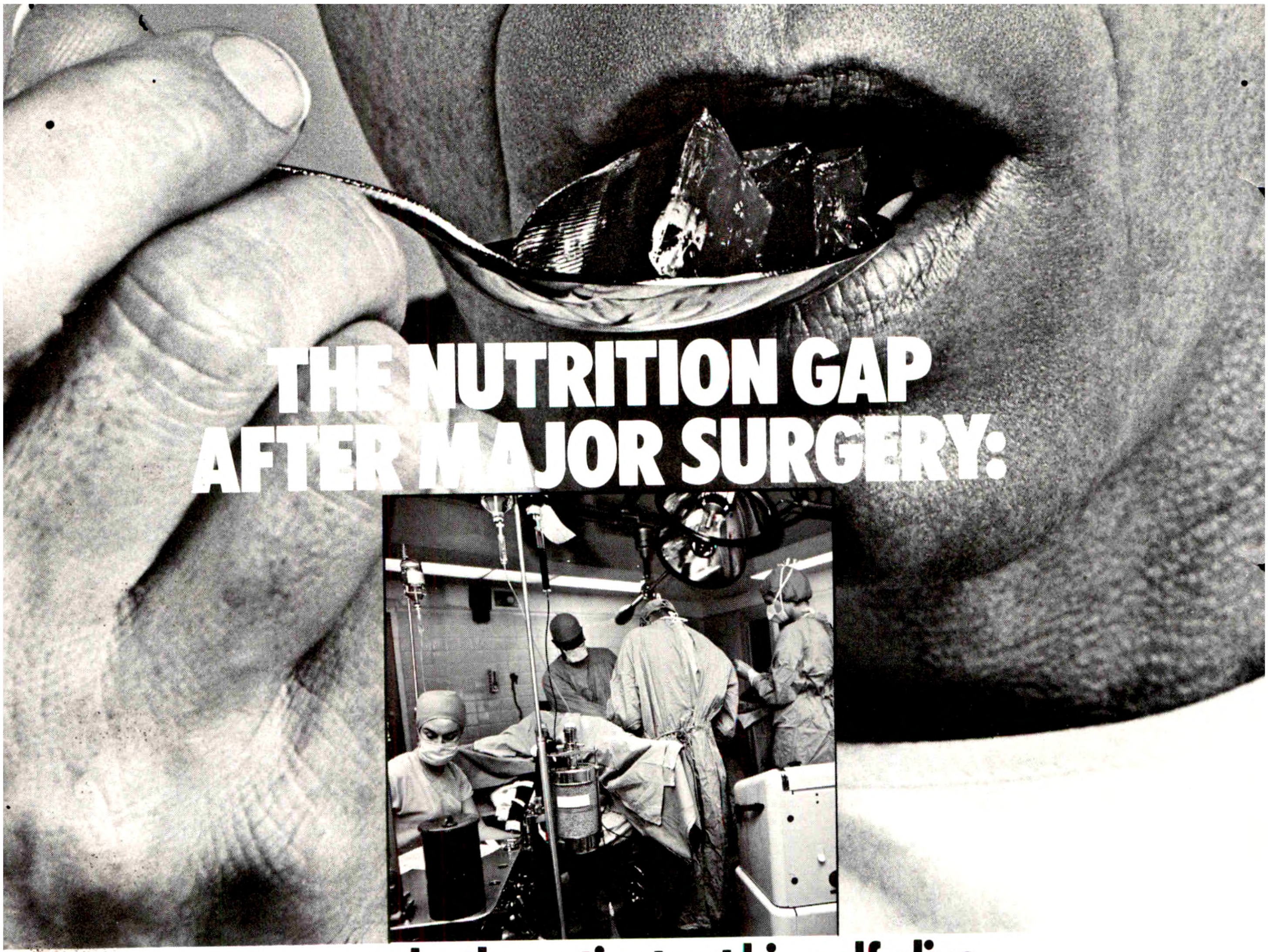
The Weavenit graft has a special warp knit structure—with more interstices—to promote fast healing. These interstices are both small enough to allow sufficient preclotting and porous enough to facilitate fast tissue ingrowth. It's easier to form a firmly adhering neo-intima.

Weavenit is a thin-walled graft, so there's minimal tissue buildup. That's important where a small diameter prosthesis is required. It assures long-term patency.

It's pliable and is easy to handle. It conforms to the anastomotic lines. What's more, Weavenit can be cut at any angle without ravelling or fraying.

Available in straight tubes, bifurcations and patches.

Meadox Medicals
P.O. Box 530, 6 Raritan Road, Oakland, New Jersey 07436
Better by Design.



THE NUTRITION GAP AFTER MAJOR SURGERY:

It can make the patient eat himself alive.

After major surgery, the patient may burn up 3000 Calories a day. Clear liquid diets given after such surgery supply a few hundred Calories... and very little else. To make up the energy deficit, patients soon start to consume their own body protein.

With Vivonex HN you can give the patient 3000 Calories, 20 grams of usable nitrogen (equal to 125 grams of usable protein), and a balanced diet of elemental nutrients each day. (Evidence of minimal G.I. function must exist.)

Vivonex HN raises total protein levels... helps restore positive nitrogen balance... helps prevent the rapid protein wastage that may retard post operative healing and recovery.

Vivonex HN is an alternative to the risks of intravenous hyperalimentation because it consists solely of basic nutrients requiring little or no digestion: pure amino acids, simple sugars, essential fat, vitamins and minerals. Absorption takes place rapidly and completely in the upper intestine. There is no indigestible matter.

Ideal for tube feeding, Vivonex HN is easily fed through small-gauge tubes. It may also be served as a drink (Vivonex HN is unflavored).

Supplied in boxes containing ten 80-gram packets of unflavored water-soluble powder providing 3000 Calories, 20 grams of usable nitrogen and a full day's balanced nutrition, including the Recommended Daily Allowances of vitamins and minerals.

Precautions: For use only under a physician's supervision. Do not administer parenterally. Because of the high caloric contribution from carbohydrates some depleted individuals may manifest elevated blood sugar levels requiring insulin for regulation. The diet should not be used by diabetics without their physician's approval. The electrolyte content of the diet is based on requirements of normal individuals and may be excessive for patients with electrolyte imbalance. Use during pregnancy or lactation may require supplemental vitamins and minerals. Use for children under ten years may require adjusting the amount consumed daily to meet the Recommended Dietary Allowance for the age group involved. Vivonex HN High Nitrogen Diet is recommended for up to two months of continuous use. Store in a cool dry place.

Are you taking advantage of these nutritional information services?

- Eaton Nutrition Teaching Films
- The Eaton Nutrition Speakers Bureau
- Eaton In-Service Programs—Nutrition
- Intake: Perspectives in Clinical Nutrition (monographs).

Detailed information about any of these programs is available from your local Eaton Representative or direct from Eaton Laboratories.

For 'round-the-clock medical consultation on Eaton products, 'phone Norwich, New York, Area Code 607-335-2111

© Morton-Norwich Products, Inc. 1972

® Originators of chemically defined diets
Eaton Laboratories
division of Morton-Norwich Products, Inc.
Norwich, New York 13815

You can help close this nutrition gap with

VIVONEX® HN ™

soluble powder The only chemically defined elemental high nitrogen diet

The only oral hyperalimentation

T.E.D.®

anti-embolism stockings

Pulmonary Embolism is a major problem in active patients suddenly confined to bed.

T.E.D. Stockings help prevent thrombosis and subsequent pulmonary embolism by providing encircling graduated compression. The construction and features in both the cotton and nylon styles, below knee and thigh length, are superior to any other anti-embolism stocking available. Let your Kendall salesman show you the differences and how you can immediately fit most patients with one of the available sizes.

He has reprints of articles on pulmonary embolism and an In-Service Program that shows the how and why of T.E.D. or write The Kendall Company, Hospital Products Division, 309 West Jackson Blvd., Chicago, IL 60606 for further information.

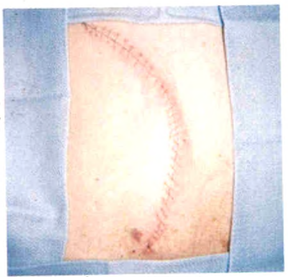
Contraindications: In patients with open ulcers, severe arteriosclerosis and other ischemic vascular diseases, and massive leg edema with imminent pulmonary edema from congestive heart disease. Any signs of irritation or redness of the skin should be carefully noted.

Caution: Federal law restricts this device to sale by or use on the order of a physician.

KENDALL
sets the pace

CURITY®

wet dressings indicated



Infected
Suture Wounds

Infiltrated I.V.'S

Decubitus Ulcers

Debridement

Easy Aseptic Application

Curity® wet dressings provide sterile, moist heat therapy for many medical conditions. Each dressing is pre-moistened and sterile in an individual foil package designed for aseptic opening and application. And Curity gives you a choice of water or normal saline solution.

The cumbersome procedure for preparing sterile wet dressings is eliminated. The Curity system saves time, facilitates sterile technique and provides hot moist dressings from the heat lamp in just 5 minutes. Ask your Kendall representative for a demonstration or write The Kendall Company, 309 West Jackson Blvd., Chicago, IL 60606.

KENDALL

sets the pace

BETADINE® "disposables"

Microbicidal power for scrubbing...for prepping

- Broad-spectrum microbicidal action promptly kills both gram-positive and gram-negative bacteria (including antibiotic-resistant strains), fungi, viruses, protozoa and yeasts.
- Virtually nonirritating . . . nonstaining to skin and natural fabrics.
- Convenient, single-use aids to surgical antisepsis.

BETADINE microbicides Chosen by NASA

*In rare instance of local irritation or sensitivity, discontinue use in the individual.

Purdue Frederick

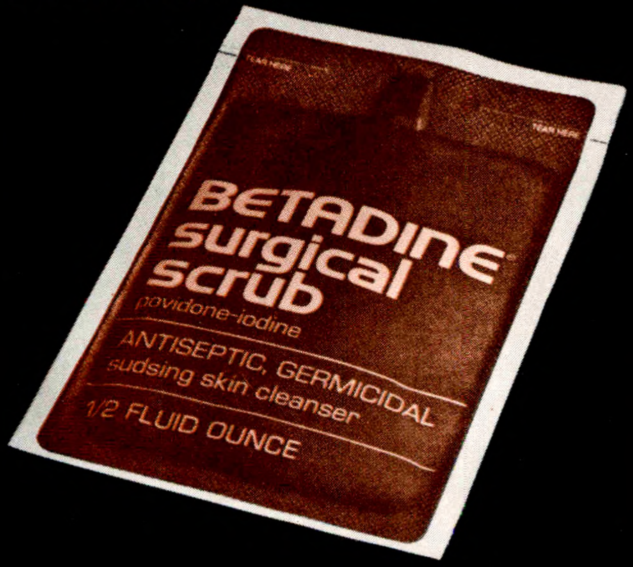
© COPYRIGHT 1973, THE PURDUE FREDERICK COMPANY/NORWALK, CONN. 06856 A7257 135073

BETADINE SURGI-PREP Sponge-Brush

The only sponge-brush or sponge with the same microbicide as in BETADINE Surgical Scrub. For preoperative scrubbing by the surgical team; general hand and skin degerming.*

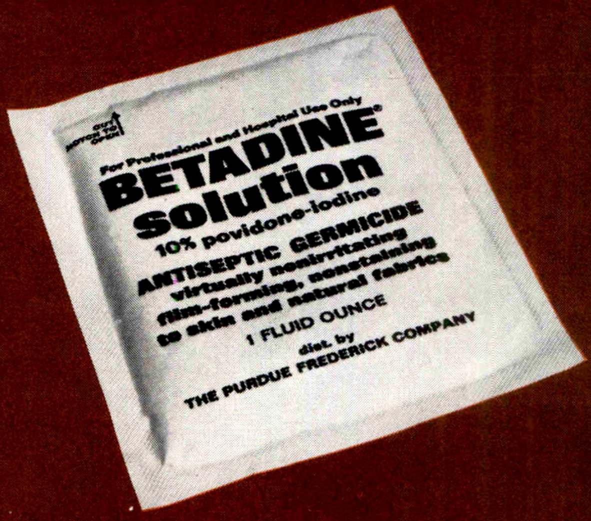
BETADINE Surgical Scrub Packette ½ oz.

For preoperative scrubbing by the surgical team; for prepping of patient's skin for surgery; for general hand and skin degerming.*

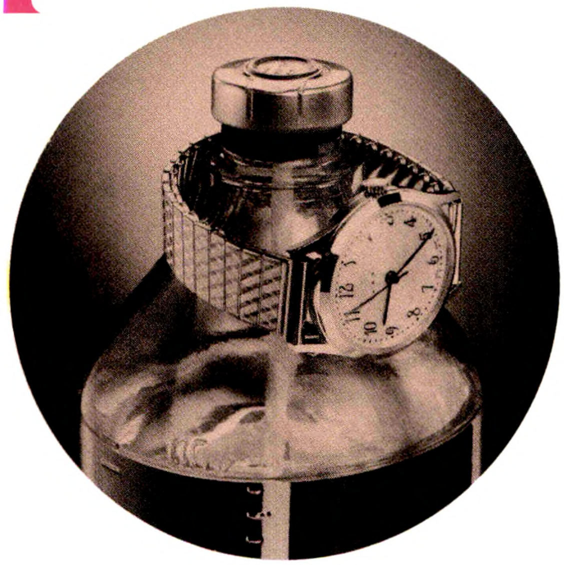


BETADINE Solution Packette 1 oz.

To enhance antisepsis by painting the operative site preoperatively and postoperatively. Maintains microbicidal action in the presence of blood, pus and serum.


For Professional and Hospital Use Only
BETADINE®
Solution
10% povidone-iodine
ANTISEPTIC GERMICIDE
virtually nonirritating
film-forming, nonstaining
to skin and natural fabrics
1 FLUID OUNCE
dist. by
THE PURDUE FREDERICK COMPANY

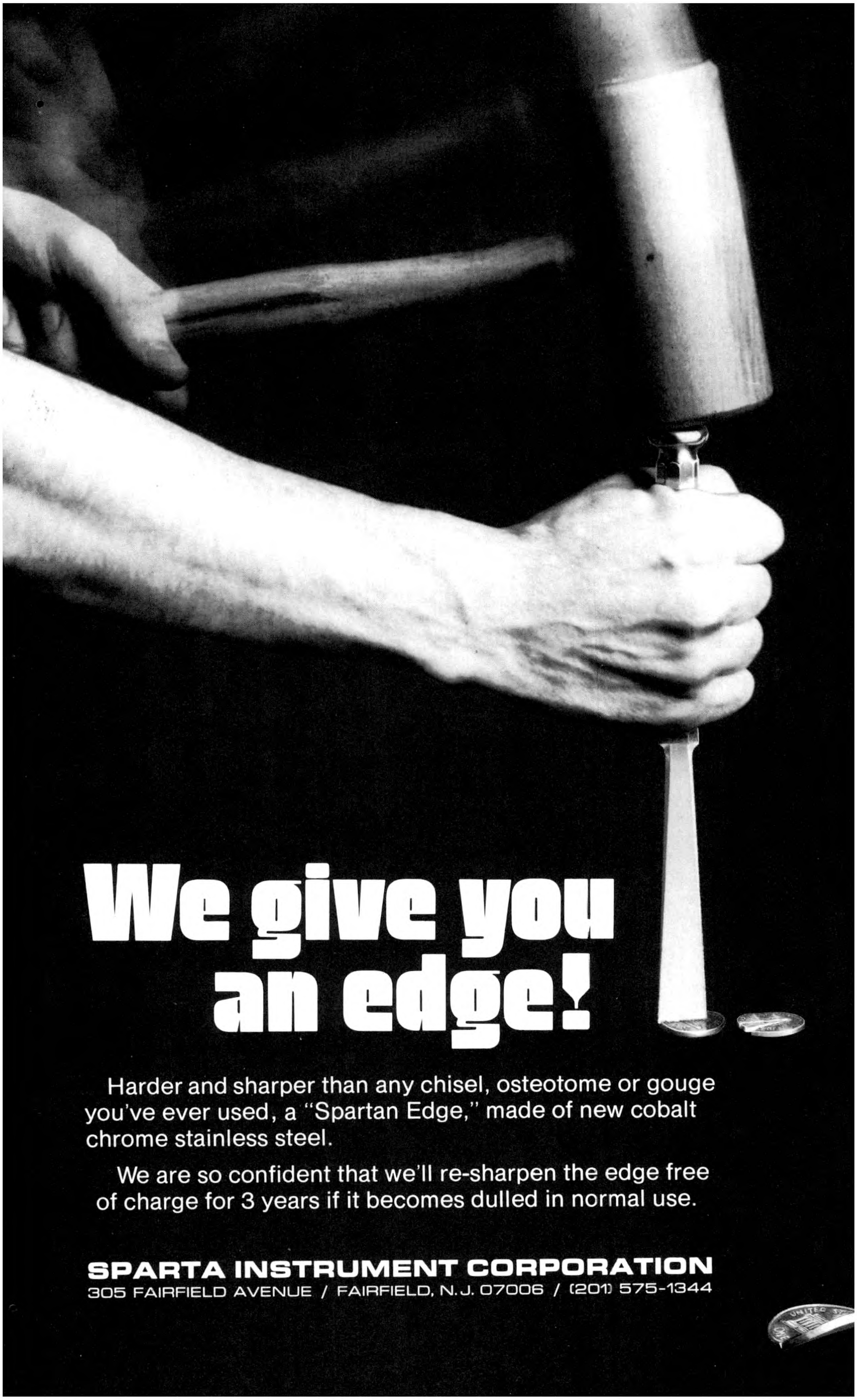
when you can retire an idea whose time has passed...



you're ready for an idea

it's time for
Viaflex®
the non-air-dependent
shatterproof IV
solution container

VIAFLEX® the hospital software from TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015



We give you an edge!

Harder and sharper than any chisel, osteotome or gouge you've ever used, a "Spartan Edge," made of new cobalt chrome stainless steel.

We are so confident that we'll re-sharpen the edge free of charge for 3 years if it becomes dulled in normal use.

SPARTA INSTRUMENT CORPORATION
305 FAIRFIELD AVENUE / FAIRFIELD, N.J. 07006 / (201) 575-1344

An important advance in cancer chemotherapy from Bristol Laboratories

new **Blenoxane**™
(sterile bleomycin sulfate)

An effective palliative agent and adjuvant to radiotherapy and surgery in selected tumors.

Please see last page for complete prescribing information.

new **Blenoxane**™
(sterile bleomycin sulfate)
A selective, antineoplastic antibiotic

Blenoxane (sterile bleomycin sulfate) is an antineoplastic formulation of bleomycin, the basic glycopeptide antibiotic isolated from a strain of *Streptomyces verticillus* in 1962. Although the exact mechanism of the agent's antitumor effect is not completely understood, it is associated with an inhibition of DNA synthesis, with some evidence of lesser inhibition of RNA and protein synthesis. Most of the clinical experience with Blenoxane reported to date has involved patients in advanced stages of cancer who had failed to respond adequately to other drugs or modes of therapy. Even in these cases, however, Blenoxane has often produced good results.

1/ in selected squamous cell carcinomas

Site	Patients Evaluable	Number of Responses
Head and neck	181	65
Larynx and paralarynx	52	16
Cervix	69	12
Vulva	13	8
Vagina	4	1
Penis	10	4
Skin	29	9

“This antibiotic has the highest rate of activity in squamous carcinoma that has so far been found for any drug, and thus offers hope of new clinical studies that can provide a basis for better therapy.” [1]

2/ in selected lymphomas

Type	Patients Evaluable	Number of Responses
Hodgkin's disease	116	49
Reticulum cell sarcoma	29	11
Lymphosarcoma	28	14
Mycosis fungoides	9	5

“Perhaps more striking is the very high incidence of prompt responses seen in advanced Stage IV Hodgkin's disease.” [2]

3/ in selected testicular carcinomas

Type	Patients Evaluable	Number of Responses
Embryonal cell carcinoma of the testes; treated with:		
bleomycin	29	13
bleomycin plus vinblastine	13	10
Choriocarcinoma of the testes; treated with:		
bleomycin	7	2
bleomycin plus vinblastine	4	3
Teratocarcinoma of the testes; treated with:		
bleomycin	12	4
bleomycin plus vinblastine	5	4
Seminoma; treated with:		
bleomycin	1	0
bleomycin plus vinblastine	1	1

“In some tumors it appears to be as good as or even more efficacious than [previously available] chemotherapy.” [3]

...with no depressant effect on hematopoietic or immunosuppressive mechanisms to date

❝The absence of toxic effects on the hematopoietic system and of any immunosuppressive action is emphasized, as this gives the drug a special importance.❞ [3]

In the past two years, over 100 clinicians have investigated the therapeutic effects of Blenoxane (sterile bleomycin sulfate). Over 1,300 patients have been treated in the major cancer care units in the United States.

These studies have shown repeatedly that Blenoxane may be active against certain tumors generally insensitive to other available agents; that it may enhance the results achieved with certain other chemotherapeutic agents; and that it may be an effective adjunct to indicated surgical procedures and radiotherapy.

They have also demonstrated the complete absence of immunosuppressive or adverse hematopoietic effects to date. Thus, Blenoxane may be potentially useful in combination with other agents, or in patients already exhibiting pancytopenia.

However, these same studies clearly indicate that Blenoxane is far from an innocuous agent. Pulmonary toxicity, occurring as pneumonitis in about ten per cent of patients, has led to pulmonary fibrosis and death even when detected in the early stages.

In addition, approximately half of the patients will exhibit some dermatological manifestations of therapy with Blenoxane. The skin reactions are usually characterized by erythema or hyperkeratosis—most often on the hands and elbows—and potentially progressive to ulceration.

Consequently, the physician will recognize that the clinical use of an agent such as Blenoxane presupposes a thorough knowledge of its potential applications, pharmacology, toxicity and clinical record—subjects which cannot be adequately reviewed in a communication of this type.

We urge those physicians who anticipate a use for Blenoxane to consult the Bristol Laboratories Introductory Monograph for information currently available on therapy with Blenoxane.

1. Ohnuma, T., as reported in: J.A.M.A. *216*:415 (Apr. 19) 1971.
2. Krakoff, I.H.: The present status of cancer chemotherapy, M. Clin. North Am. *55*:683 (May) 1971.
3. Clinical Screening Cooperative Group of the European Organization for Research on the Treatment of Cancer. Brit. M.J. *2*:643 (June 13) 1970.

new **Blenoxane**™ *(sterile bleomycin sulfate)*

Please see last page for complete prescribing information.

new **Blenoxane**™ *(sterile bleomycin sulfate)*.

BLENOXANE™ (sterile bleomycin sulfate)
3010DIRO-03 May 1973

> **WARNING.** It is recommended that Blenoxane be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Since facilities for necessary laboratory studies must be available, hospitalization of patients is recommended.
>
> Pulmonary fibrosis is the most serious toxicity with Blenoxane. (See "Adverse Reactions" section.)
>
> In the treatment of each patient, the physician must weigh carefully the possibility of achieving therapeutic benefit with the risk of toxicity.
>
> In 1% of patients, a hypersensitivity reaction, similar to anaphylaxis clinically, occurred, particularly in lymphoma patients. This has resulted in death.
>
> The reaction which may be immediate or after several hours delay, occurs only after the first or second dose. It consists of hypotension, fever, chills, mental confusion, and wheezing.
>
> **Usage in Pregnancy**—Safe use of Blenoxane in pregnant women has not been established. Therefore the benefits to the patient should be weighed against the potential toxicity to fetus or embryo.

DESCRIPTION. Blenoxane (sterile bleomycin sulfate) is composed of basic cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus*. It is highly soluble in water.

ACTION. Although the exact mechanism of action of Blenoxane is unknown, available evidence would seem to indicate that the main mode of action is the inhibition of DNA synthesis with some evidence of lesser inhibition of RNA and protein synthesis.

In mice, high concentrations of Blenoxane are found in the skin, lungs, kidneys, peritoneum and lymphatics. Tumor cells of the skin and lungs have shown a strong affinity for Blenoxane in contrast to the lack of affinity of hematopoietic tissue. This selective affinity of the drug for different sites and cell types creates a better understanding of the therapeutic benefits and the toxicity of Blenoxane.

20 to 40% of an administered dose in humans is recovered in the urine as active bleomycin.

INDICATIONS. Blenoxane should be considered a palliative treatment and/or adjuvant to surgery and radiation therapy. It has been shown to be useful in the management of the following neoplasms:

Squamous Cell Carcinoma—head and neck including mouth, tongue, tonsil, nasopharynx, oropharynx, sinus, palate, lip, buccal mucosa, gingiva and epiglottis; skin; larynx and paralarynx; penis; cervix; vulva. The response to Blenoxane is poorer in patients with head and neck cancer which has been irradiated previous to Blenoxane therapy.

Lymphomas—Hodgkins, reticulum cell sarcoma, lymphosarcoma. It is of special note that most of the Hodgkins patients treated to date had disseminated disease (Stage IV) no longer treatable by bone marrow depressant agents.

Testicular Carcinoma—embryonal cell, choriocarcinoma, and teratocarcinoma. Studies to date have revealed that the use of vinblastine sulfate with Blenoxane increases the response rate of testicular tumors.

Other—Blenoxane has been shown to produce responses in some renal carcinomas, soft tissue sarcomas, and in the prevention of pleural fluid accumulation when administered intrapleurally.

CONTRAINDICATIONS. Blenoxane is contraindicated in patients who have demonstrated a hypersensitivity to it in the past.

The physician must weigh carefully the therapeutic benefit versus risk of toxicity which may occur.

PRECAUTIONS. Blenoxane should be administered preferably to patients who are hospitalized and who can be observed carefully and frequently during and after therapy. It should be used with extreme caution in patients with significant impairment of renal function or compromised pulmonary function due to disease other than malignancy.

To monitor the onset of pulmonary toxicity, roentgenograms of the chest should be taken every 1 to 2 weeks. If pulmonary changes are noted, treatment should be discontinued until it can be determined whether the cause is drug related. Pneumonitis due to Blenoxane should be treated with corticosteroids in an effort to prevent progression to pulmonary fibrosis. Infectious pneumonitis should receive appropriate antibiotic therapy.

ADVERSE REACTIONS. Skin—Skin changes were the most frequent side effect occurring in approximately 52.3% of treated patients. These consisted of mouth ulcers, alopecia, hyperpigmentation, thickening, ulceration, redness, hyperkeratosis, nail changes, rash, vesiculation, tenderness, pruritus, hyperesthesia, peeling, stria, and bleeding. In only 0.2% of treated patients was it necessary to discontinue Blenoxane therapy because of skin toxicity.

Skin toxicity was a relatively late manifestation developing usually in the 2nd and 3rd week of treatment after 150 to 200 units of Blenoxane (sterile bleomycin sulfate) had been administered and, in general, was related to total cumulative dose.

Pulmonary—This is potentially the most serious side effect, occurring in approximately 10% of treated patients. The most frequent manifestation is pneumonitis occasionally progressing to pulmonary fibrosis which may result in death. Approximately 1% of patients treated died of pulmonary fibrosis. An analysis of the data revealed that pulmonary toxicity is usually both dose and age related, being more common in patients over 70 years of age receiving over 400 units total dose. However, this toxicity is unpredictable and has been seen occasionally in young patients receiving low doses.

The identification of patients with pulmonary toxicity due to Blenoxane has been extremely difficult. The reason for this is the lack of specificity of the clinical syndrome, the x-ray changes and even the tissue changes seen on examination of biopsy and autopsy specimens.

Blenoxane-induced pneumonitis apparently produces dyspnea and fine rales that are in no way different from those produced by infectious pneumonias, or the signs and symptoms produced by primary or metastatic lung disease in some patients.

On x-ray, Blenoxane-induced pneumonitis produces patchy opacities, usually of the lower lung fields, that look the same as infectious bronchopneumonia or even lung metastases in some patients.

The microscopic tissue changes due to Blenoxane toxicity are frequently present as bronchiolar squamous metaplasia, reactive macrophages, atypical alveolar epithelial cells, fibrinous edema, and interstitial fibrosis. The acute stage may involve capillary changes and subsequent fibrinous exudation into alveoli producing a change similar to hyaline membrane formation and progressing to a diffuse interstitial fibrosis resembling the Hamman-Rich syndrome.

These microscopic findings are non-specific and are similar to the changes produced in radiation pneumonitis, pneumocystic pneumonitis, and at times reaction to long-standing malignant pulmonary disease.

Serial pulmonary function tests in 156 patients receiving Blenoxane therapy revealed some demonstrable alteration in approximately 20%. The most common changes were a decrease in total lung volume and a decrease in vital capacity. However, no predictive correlation between these changes and the development of pulmonary fibrosis could be ascertained.

Other—Fever, chills, nausea, and vomiting were also frequent side effects. Pain at tumor site, phlebitis, and other local reactions were reported infrequently.

Toxicity to the renal, hepatic, and CNS may occur at any time after initiation of therapy and, as with any potent drug, these systems should be monitored.

It is noteworthy that there has been no evidence of bone marrow or immunological depression to date. This is contrary to the currently available antineoplastic drugs.

Anorexia and weight loss are common and may persist long after termination of this medication. Since these signs and symptoms occur with malignancy, it may be difficult to evaluate the role of Blenoxane.

DOSAGE. The following dose schedule is recommended: **Squamous cell carcinoma, lymphosarcoma, reticulum cell sarcoma, testicular carcinoma**—0.25 to 0.50 units/Kg. (10 to 20 units/M^2) given intravenously or intramuscularly weekly or twice weekly.

Hodgkins Disease—0.25 to 0.50 units/Kg. (10 to 20 units/M^2) intravenously or intramuscularly weekly or twice weekly. After a 50% response, the maintenance dose of 1 unit daily or 5 units weekly intravenously or intramuscularly should be given.

Because of the possibility of anaphylaxis, all lymphoma patients should be started with 5 units or less for the first 2 doses. If no acute reaction occurs, then the regular dosage schedule may be followed.

Toxicity of Blenoxane appears to be dose-related with a striking increase when the total dose is over 400 units. Total doses over 400 units should be given with great caution.

Hodgkins and testicular improvement are prompt and noted within two weeks. If no improvement is seen by this time, chances of improvement are very low. Squamous cell cancers respond more slowly, sometimes requiring as long as three weeks before improvement is noted.

ADMINISTRATION. Blenoxane may be given by the intramuscular, intravenous, intra-arterial, or subcutaneous routes.

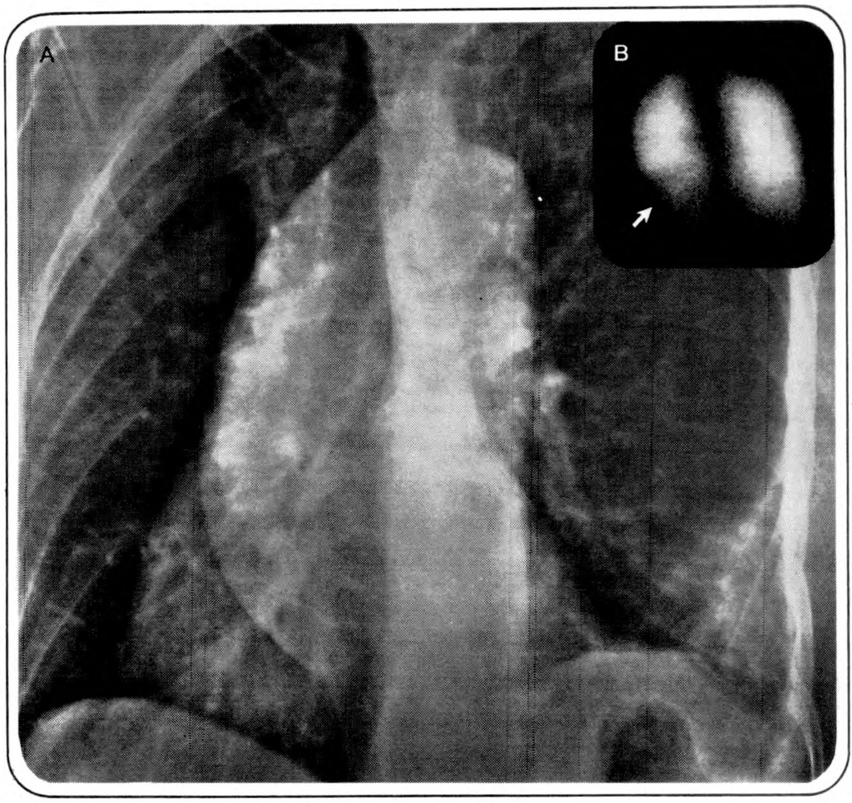
Intramuscular or Subcutaneous—Dissolve the contents of a Blenoxane ampule in 1 to 5 ml. of Sterile Water for Injection, U.S.P., Sodium Chloride for Injection, U.S.P., or 5% Dextrose in Water.

Intravenous or Intra-arterial—Dissolve the contents of the ampule in 5 ml. or more of a solution suitable for injection, e.g., physiologic saline or glucose, and administer slowly over a period of ten minutes.

SUPPLY. Each ampule contains 15 units of Blenoxane as sterile bleomycin sulfate. ***NDC*-0015-3010.**

BRISTOL LABORATORIES **BRISTOL** Division of Bristol-Myers Company/Syracuse, New York 13201

pulmonary
infarction
or pneumonia*?



In any case...
when nutritional
supplementation
is indicated

Berocca® is therapy
tablets

With balanced, high potency B-complex and C vitamins... No odor... Virtually no aftertaste... Lowest priced Rx formula.

Please see complete product information, a summary of which follows:

Each Berocca Tablet contains:

Thiamine mononitrate (Vitamin B_1)	15 mg
Riboflavin (Vitamin B_2)	15 mg
Pyridoxine HCl (Vitamin B_6)	5 mg
Niacinamide	100 mg
Calcium pantothenate	20 mg
Cyanocobalamin (Vitamin B_{12})	5 mcg
Folic acid	0.5 mg
Ascorbic acid (Vitamin C)	500 mg

Indications: Nutritional supplementation in conditions in which water-soluble vitamins are required prophylactically or therapeutically.

Warning: Not intended for treatment of pernicious anemia or other primary or secondary anemias. Neurologic involvement may develop or progress, despite temporary remission of anemia, in patients with pernicious anemia who receive more than 0.1 mg of folic acid per day and who are inadequately treated with vitamin B_{12}.

Dosage: 1 or 2 tablets daily, as indicated by clinical need.

Available: In bottles of 100 and 500.

ROCHE

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

*(A.) AP film of the chest with the patient in right lateral decubitus position demonstrates a wedge-shaped infiltrate in the left lower lung field. (B.) Posterior perfusion scan of the lungs demonstrates a defect in the left lung (arrow) at the left base in the same area as the infiltrate on the chest film. The wedge configuration in both studies suggests pulmonary infarction secondary to embolization although pneumonia and infarct may give similar appearances.

touch . . . and go

When a Dulcolax suppository puts its gentle touch on the colon, normal peristalsis begins throughout the large intestine, with evacuation often in as few as 15 minutes. Dulcolax lets you or your patient dictate the time and the place. And almost anyone can take Dulcolax – its only contraindication is acute surgical abdomen.

Dulcolax®

bisacodyl NF

Suppositories...to replace the enema

Boehringer Ingelheim

BOEHRINGER INGELHEIM

Boehringer Ingelheim Ltd.
Elmsford, N.Y. 10523

Progress in Surgery

Editorial Board:
M. Allgöwer (Basel); *S.-E. Bergentz* (Malmö)
R. Y. Calne (Cambridge); *U.F. Gruber* (Basel)

This series of annual volumes assists general and specialized surgeons in staying informed on 'what's new in surgery' by providing original reviews from outstanding experts in their respective fields as well as frequent discussions of controversial themes by authorities expressing differing viewpoints.
The editorial board, in preparing the annual volume, selects several papers on subjects of general interest where important discoveries have recently been reported or new insight into diagnosis or therapy have brought about direct and immediate consequences for the surgeon's daily work. In sum, basic knowledge in addition to technical know-how at the post-graduate level is transmitted through the richly-illustrated volumes of 'Progress in Surgery'.

Selected Contributions Already Published in the Series
Crohn's Disease, with Special Reference to Surgical Management
Goligher, J.C., De Dombal, F.T. and *Burton, I.*
New Aspects of the Pathogenesis of Thrombo-Embolism
Nilsson, I.M. and *Isacson, S.*
Atelectasis in the Surgical Patient. Recent Conceptual Advances
Laver, M.B. and *Bendixen, H.H.*
Strictures of Bile Ducts
Smith, R.
Pathophysiological Aspects on Surgical Treatment of Thyroid Disease
Heimann, P.

For further information please request a detailed prospectus

S. Karger AG
Arnold-Böcklin-Strasse 25
CH–4011 Basel (Switzerland)

S.Karger **Basel** **München** **Paris** **London** **New York** **Sydney**

new Santyl® ointment (collagenase)

Indications: Santyl Ointment is indicated for debriding dermal ulcers and severely burned areas. In other types of necrotic skin lesions reports on the use of Santyl Ointment have been limited to clinical observations without controls.

Contraindications: Application is contraindicated in patients who have shown local or systemic hypersensitivity to Collagenase.

Precautions: The enzyme's optimal pH range is 7 to 8. Lower pH conditions have a definite adverse effect on the enzyme's activity, and appropriate precautions should be taken.

The enzymatic activity is also adversely affected by detergents and hexachlorophene and heavy metal ions such as mercury and silver which are used in some antiseptics. When it is suspected such materials have been used, the site should be carefully cleansed by repeated washings with normal saline before Santyl Ointment is applied. Soaks containing metal ions or acidic solutions such as Burow's solution should be avoided because of the metal ion and low pH. Cleansing materials such as hydrogen peroxide or Dakin's solution do not interfere with the activity of the enzyme.

Debilitated patients should be closely monitored for systemic bacterial infections because of the theoretical possibility that debriding enzymes may increase the risk of bacteremia.

The ointment should be confined to the area of the lesion in order to avoid the risk of irritation or maceration of normal skin.

A slight erythema has been noted occasionally in the surrounding tissue particularly when the enzyme ointment was not confined to the lesion. This can be readily controlled by protecting the healthy skin with a material such as Lassar's paste.

Since the enzyme is a protein, sensitization may develop with prolonged use although none has been observed to date.

Adverse Reactions: Adverse reactions to Collagenase have not been noted when used as directed.

Dosage & Administration: Santyl Ointment should be applied once daily (or once every other day in the case of outpatients) in the following manner.

(1) Prior to application the lesions should be gently cleansed with a gauze pad saturated in normal saline, buffer (pH 7.0-7.5) or hydrogen peroxide to remove any film and digested material.

(2) Whenever infection is present, as evidenced by positive cultures, pus, inflammation or odor, it is desirable to use an appropriate topical antibacterial agent. Neomycin-Bacitracin-Polymyxin B (Neosporin) has been found compatible with Santyl Ointment. This antibiotic should be applied to the lesion in powder form or solution prior to the application of Santyl Ointment. Should the infection not respond, therapy with Santyl Ointment should be discontinued until remission of the infection.

(3) Santyl Ointment should be applied (using a wooden tongue depressor or spatula) directly to deep wounds, or, when dealing with shallow wounds, to a sterile gauze pad which is then applied to wound. The wound is covered with sterile gauze pad and secured with clear tape or Kling bandage.

(4) Crosshatching thick eschar with a #11 blade is helpful. It is also desirable to remove as much loosened detritus as can be done readily with forceps and scissors.

(5) All excess ointment should be removed each time dressing is changed.

(6) Use of the ointment should be terminated when sufficient debridement of necrotic tissue has taken place.

Overdose: Action of the enzyme may be stopped, should this be desired, by the application of Burow's solution U.S.P. (pH 3.6-4.4) to the lesion.

How Supplied: Santyl Ointment contains 250 units of Collagenase enzyme per gram of white petrolatum U.S.P. The potency assay of Collagenase is based on the digestion of undenatured collagen (from bovine Achilles tendon) at pH 7.2 and 37° C. for 24 hours. The number of peptides cleaved are measured by reaction with ninhydrin. Peptides released by a trypsin digestion control are subtracted. One net Collagenase unit will solubilize ninhydrin reactive material equivalent to 4 micromoles of Leucine.

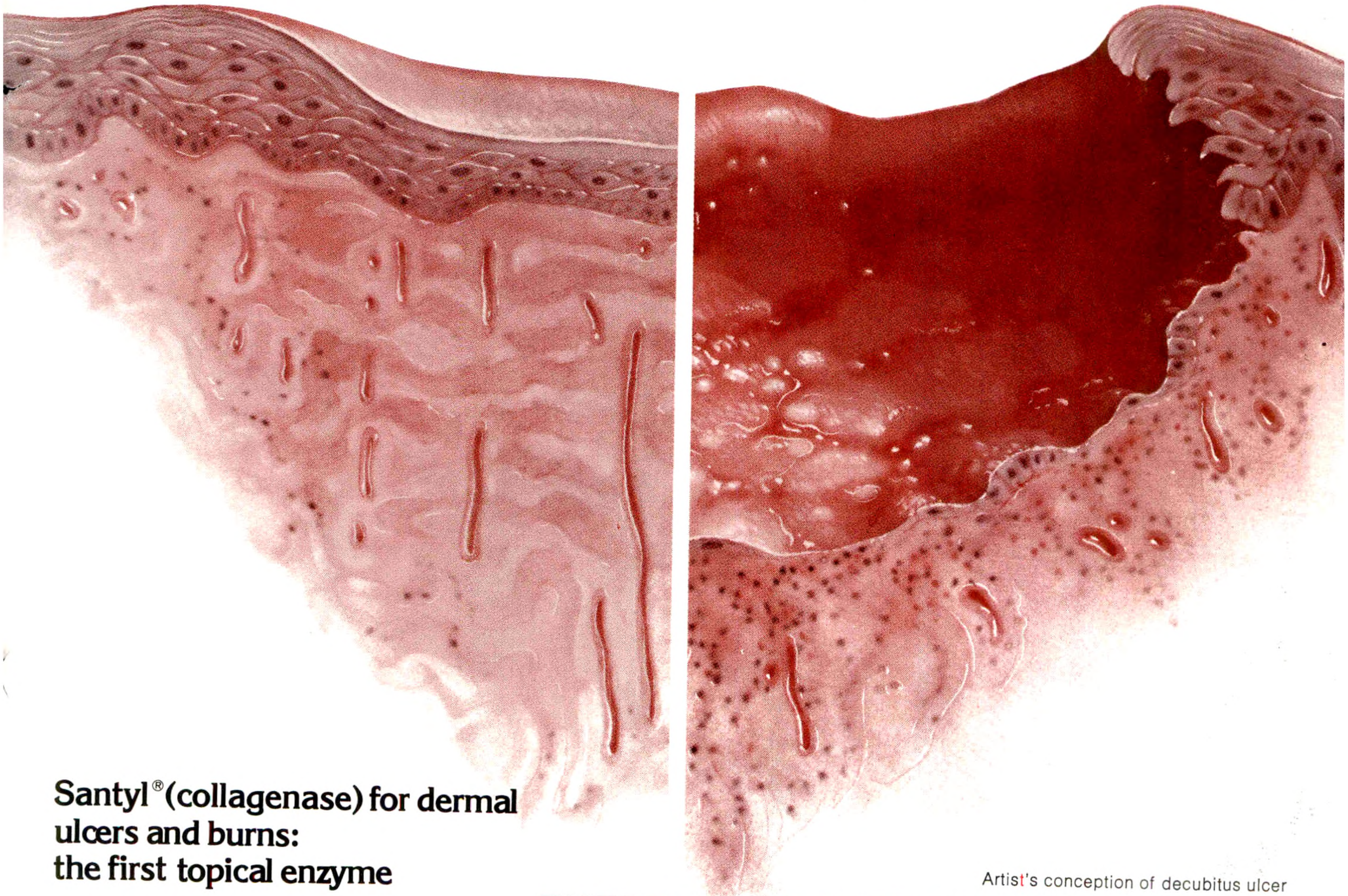
Knoll Pharmaceutical Co.
30 North Jefferson Road
Whippany, New Jersey 07981

new **Santyl**®
ointment
(collagenase)

"...it may prove to be the drug of choice for wound debridement."

Varma A O *et al: Surg. Gynec. Obstet.* 136:281, Feb. 1973.

To permit healing like this...you want to start like this.



Artist's conception of decubitus ulcer

Santyl®(collagenase) for dermal ulcers and burns: the first topical enzyme

- **to attack**
  native collagen, a substance that is ordinarily resistant to all common topical enzymes used in wound debridement
- **to dissolve**
  the strands of tissue that "anchor" necrotic debris and burn eschar to the wound surface
- **to effectively remove**
  the debris that hinders healing...with simple, once-a-day application

I treat patients with dermal ulcers and burns, and I would like to receive:
☐ clinical reprints and scientific information on Santyl.
☐ a free in-service training program on the use of Santyl.

Name

Nursing home or hospital affiliation

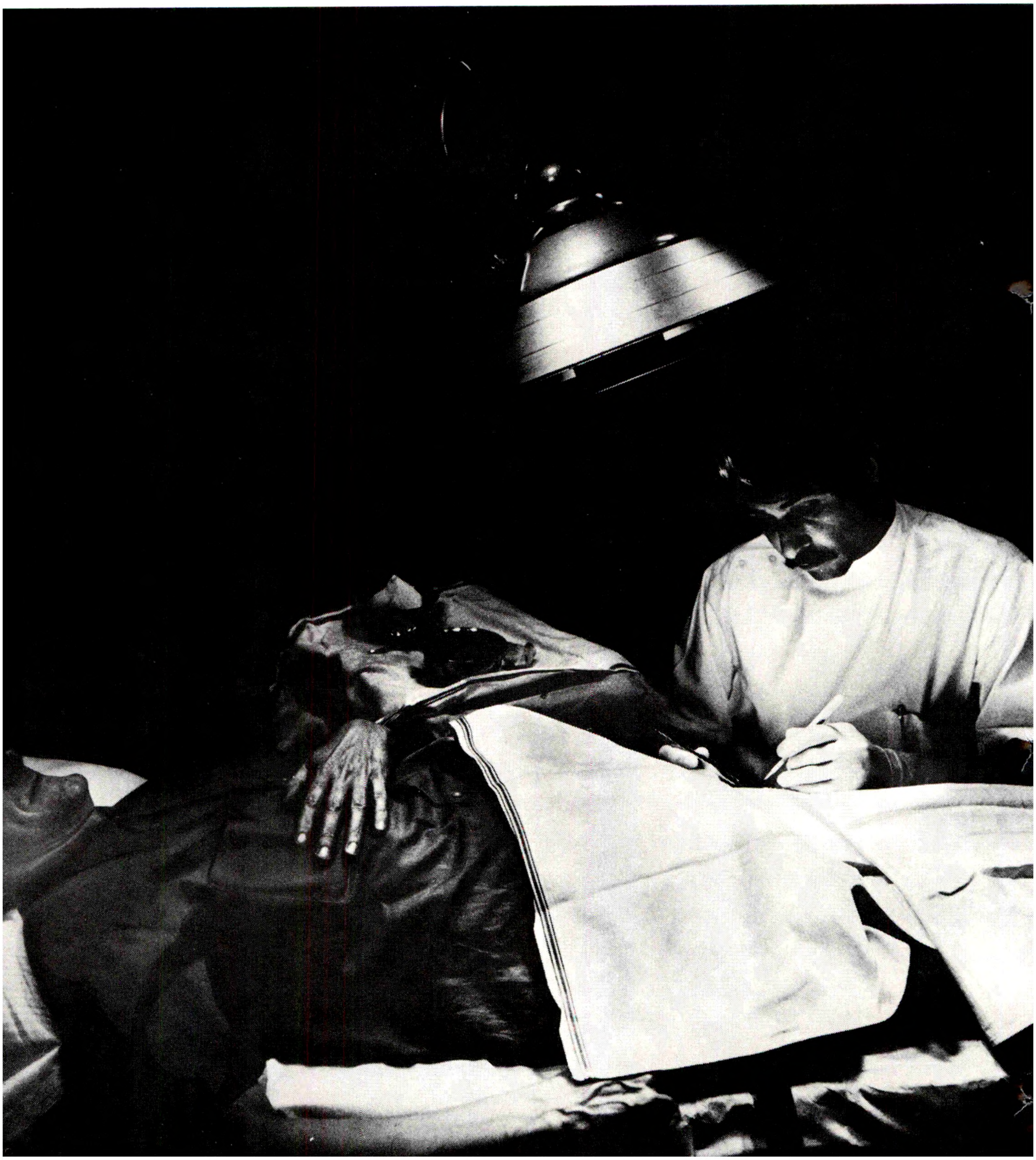
Office address

City State Zip code

Traumatic wounds

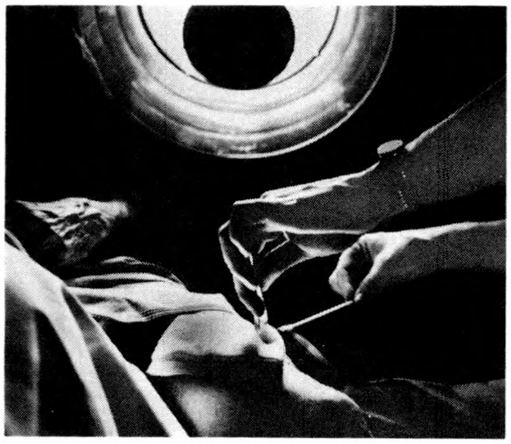
complicated by infection*–an urgent concern

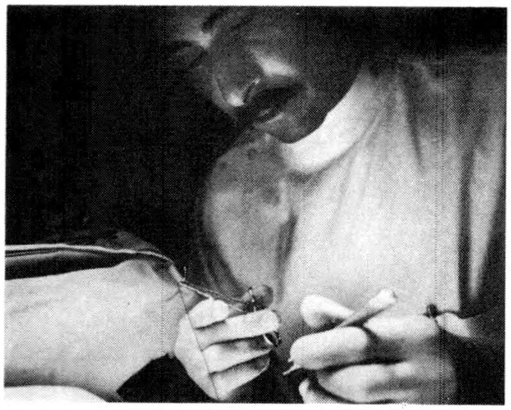
*due to susceptible organisms

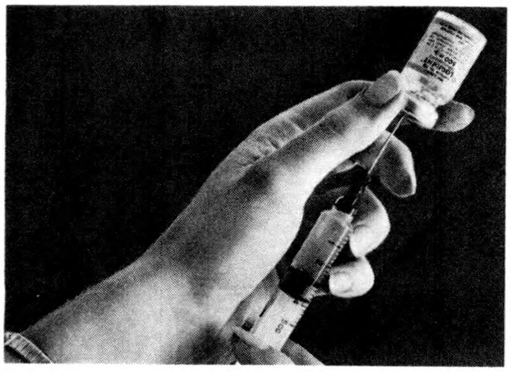


Loridine® I.M. (cephaloridine) 500-mg. ampoule

therapy worthy of consideration







Traumatic wound infections often require the rapid and effective action that Loridine I.M. can provide when they are due to susceptible organisms.

Loridine is active in vitro against many pathogens that may cause skin and soft-tissue infections, including susceptible strains of staphylococci, *Escherichia coli,* and streptococci, and is also effective in the presence of mixed infections.†

Peak blood levels of 7 to 14 mcg. per ml. respectively were obtained in one-half to one hour following intramuscular administration of 250 and 500 mg. to humans. Measurable levels of Loridine persisted for longer than twelve hours.

These are a few of many reasons why Loridine provides therapy worthy of consideration.

†Many strains of enterococci are relatively resistant. Some strains of staphylococci are resistant. *Pseudomonas* organisms are resistant, as are most indole-producing *Proteus* species and motile *Enterobacter* species.

300491

Before Administration of Loridine

1. Determine renal status before *initiating* therapy.
2. In patients with renal impairment, reduced dosage should be employed. Other antibiotic therapy should be considered if impairment is due to acute tubular necrosis.
3. As with other antibiotics, appropriate specimens for culture and susceptibility testing should be obtained.
4. Use cautiously with other potentially nephrotoxic antibiotics (e.g., gentamicin, kanamycin, colistin, and polymyxin B), in penicillin-allergic patients, and in those receiving potent diuretics, such as furosemide or ethacrynic acid.

During Administration of Loridine

1. Because of potential nephrotoxicity, daily dosages above 4 Gm. are not recommended for patients with normal renal function. The usual range for adults is 1.5 to 3 Gm. daily. In patients with renal impairment, recommendations in the package literature should be followed for *maintenance dosage* after a loading dose of 500 mg. to 1 Gm. If an endogenous creatinine clearance is considered more desirable than available BUN or serum creatinine concentrations for establishing the maintenance dosage, the initial loading dose may be given and results of that test obtained during the ensuing six or eight hours. If renal function improves during therapy, readjustment of dosage may be desirable.
2. Maintain proper hydration.
3. Monitor renal status. Renal impairment may be indicated by the appearance of urinary casts, proteinuria, oliguria, a rising BUN or serum creatinine, or a decreasing creatinine clearance or urine/plasma creatinine ratio.
4. If impaired renal function develops or worsens during therapy, discontinue use.

Please turn page for prescribing information.

Loridine® I.M. (cephaloridine)

Because of nephrotoxicity (e.g., tubular necrosis) of cephaloridine in dosages above 4 Gm. daily (see Warnings and Adverse Reactions), recommended doses should not be exceeded. Renal status of the patient should be determined prior to initiation of therapy. Patients with known or suspected impairment of renal function should be under close clinical observation for changes in renal function or be hospitalized, and reduced dosage should be employed. If impaired renal function develops during therapy, cephaloridine should be discontinued.

Actions: *Human Pharmacology*—Peak blood levels of 7 and 14 mcg. per ml. respectively were obtained in one-half to one hour following intramuscular doses of 250 and 500 mg. in humans. Measurable levels of cephaloridine persisted for longer than twelve hours.

Loridine is excreted unchanged largely by glomerular filtration. Doses of 250 and 500 mg. produced very high antibacterial concentrations in the urine, in some instances approaching 1,000 mcg. per ml.

Its nucleus and degradation products differ from those of penicillin. However, some patients who are allergic to penicillin or to other cephalosporins may also be allergic to Loridine.

Microbiology—The in-vitro bactericidal action of Loridine results from inhibition of cell-wall synthesis. It is not bound significantly to plasma protein.

Loridine is active against the following organisms in vitro:

- Beta-hemolytic and other streptococci (many strains of enterococci, e.g., *Streptococcus faecalis,* are relatively resistant)
- Staphylococci, both coagulase-positive and coagulase-negative (some strains of staphylococci are resistant to cephaloridine)
- Pneumococci
- Gonococci
- *Hemophilus influenzae*
- *Escherichia coli* and other coliform bacteria
- *Klebsiella*
- *Proteus mirabilis*

Loridine is active against *Treponema pallidum* in animal studies.

All tested strains of group A streptococci, pneumococci, and penicillin-G-susceptible staphylococci are susceptible to Loridine. However, some strains of penicillinase-producing staphylococci are resistant in vitro to concentrations of Loridine that can be achieved in the serum. The majority of strains of *H. influenzae, Pr. mirabilis, Esch. coli,* and *Klebsiella* are also susceptible in vitro.

Pseudomonas organisms are resistant to Loridine, as are most indole-producing *Proteus* species and motile *Enterobacter* species.

Indications: Loridine is indicated in the treatment of serious infections of the respiratory tract, genito-urinary tract, bones and joints, bloodstream, soft tissue, and skin due to susceptible strains of the organisms listed above. It is also indicated for therapy of early syphilis when penicillin may be contraindicated. (*See* Warnings in regard to cross-sensitivity with penicillin.) It is indicated in the treatment of gonorrhea when penicillin is not considered the drug of choice.

Appropriate culture and susceptibility studies should be performed. If the susceptibility tests show that the causative organism is resistant to Loridine, other appropriate antibiotic therapy should be instituted.

Contraindications: Loridine is contraindicated in those persons who have shown hypersensitivity to it or other cephalosporins.

Warnings: **IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN C DERIVATIVES SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS. INSTANCES OF PATIENTS WHO HAVE HAD SEVERE REACTIONS TO BOTH DRUGS, INCLUDING DEATH FROM ANAPHYLAXIS, HAVE BEEN REPORTED.**

Impairment of renal function during treatment may be indicated by the appearance of casts in the urine, proteinuria, falling urinary output, a rising BUN or serum creatinine, or a decreasing creatinine clearance or urine/plasma creatinine ratio.

Cephaloridine should be given cautiously when used with other antibiotics having nephrotoxic potential, e.g., gentamicin, kanamycin, polymyxin B, and colistin.

The results of experimental studies in animals suggest that the concurrent use of potent diuretics, such as furosemide or ethacrynic acid, may increase the risk of renal toxicity.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions: In the case of infections due to beta-hemolytic streptococci, antibiotic therapy should be continued for at least ten days.

In the therapy of gonorrhea, patients in whom there is reason to suspect concomitant syphilis should have dark-field examinations of all suspect lesions before treatment and monthly serologic tests for a minimum of three months.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Superinfections may develop with organisms not in the spectrum of Loridine, particularly *Pseudomonas*. These can be recognized by clinical observation and by means of appropriate cultures. If they occur, proper therapeutic measures should be taken.

Since safety for use in premature infants and in infants under one month of age has not been established, administration of cephaloridine to these patients is not recommended.

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest® tablets but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: *Hypersensitivity*—Maculopapular and erythematous rashes, urticaria, and anaphylaxis have been reported. Drug fever and eosinophilia also have been noted. Hypersensitivity reactions are more likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—Neutropenia and leukopenia have been reported. Some individuals have developed positive direct Coombs tests during therapy.

Liver—Transient elevations of transaminase and alkaline phosphatase levels have been noted. The significance of these findings is uncertain.

Renal—Severe, acute renal failure, in some cases terminating in death, has occurred in a small number of patients receiving Loridine. The possibility of this complication seems to be greater in seriously ill patients given more than recommended doses. Acute tubular necrosis has been noted in affected patients coming to autopsy.

Local Reactions—Pain on I.M. injection of Loridine is rare, and phlebitis on I.V. injection occurs infrequently.

Other—Nausea and vomiting have been reported.

Administration and Dosage: Ampoules should be protected from light. Extemporaneous mixtures of Loridine with other antibiotics are not recommended.

Loridine should be dissolved in either Sodium Chloride Injection or Sterile Water for Injection (*see* the package literature for dilution table).

Intramuscular Injection—Loridine is usually injected into a large muscle mass, for example, the gluteal region or the lateral aspect of the thigh.

The usual adult dosage for many infections of moderate severity is 500 mg. to 1 Gm. three times a day at equally spaced intervals. Milder and more susceptible infections have been treated with 250 to 500 mg. given two or three times a day. More severe infections may be treated with 500 mg. to 1 Gm. four times a day.

A single 2-Gm. dose is recommended for the treatment of acute gonorrhea.

Early syphilis may be treated with 500 mg. to 1 Gm. daily for ten to fourteen days.

Although some clinical experience with high doses for life-threatening conditions has been reported, it has been shown that excessive dosages (above 4 Gm. daily) may cause serious nephrotoxic reactions. For this reason, Keflin® (sodium cephalothin, Lilly) may be preferred when doses larger than 4 Gm. daily are considered for life-threatening situations. If more than 2 Gm. of cephaloridine is injected daily, the patient should be under close clinical observation for changes in renal function or be hospitalized. In addition, reduced dosage should be employed in patients with known or suspected renal impairment (*see* the package literature).

In children, a daily total of 30 to 50 mg. per Kg. (15 to 25 mg. per pound) of body weight, given in divided doses, has been found effective for mild to moderately severe infections. A daily total of 100 mg. per Kg. (50 mg. per pound) of body weight (not to exceed recommended adult doses) may be needed for very severe infections. Since safety for use in premature infants and in infants under one month of age has not been established, the use of cephaloridine in these patients is not recommended.

In both adults and children, failures have appeared to be related more closely to insusceptibility of the organism or poor general condition of the patient than to inadequate dosage.

Intravenous Injection—In the presence of extremely serious infections (such as bacteremia) or when any infection seems overwhelming, intravenous administration may be indicated.

Total daily dosages are the same as with intramuscular injection. For very susceptible organisms, 500 mg. to 1.5 Gm. per day may suffice; for less susceptible organisms and for serious infections, 2 to 4 Gm. per day may be needed.

How Supplied: Ampoules Loridine® (cephaloridine, Lilly), as follows:

250 mg., 5-ml. size, rubber-stoppered, in packages of 50 (No. 771) accompanied by six 20-ml. ampoules of Bacteriostatic Sodium Chloride Injection, U.S.P.

500 mg., 5-ml. size, rubber-stoppered, in packages of 1 (No. 722); also available in packages of 50 (No. 772) accompanied by six 20-ml. ampoules of Bacteriostatic Sodium Chloride Injection, U.S.P.

1 Gm., 10-ml. size, rubber-stoppered, in packages of 1 (No. 723); also available in packages of 25 (No. 773) accompanied by four 20-ml. ampoules of Bacteriostatic Sodium Chloride Injection, U.S.P.

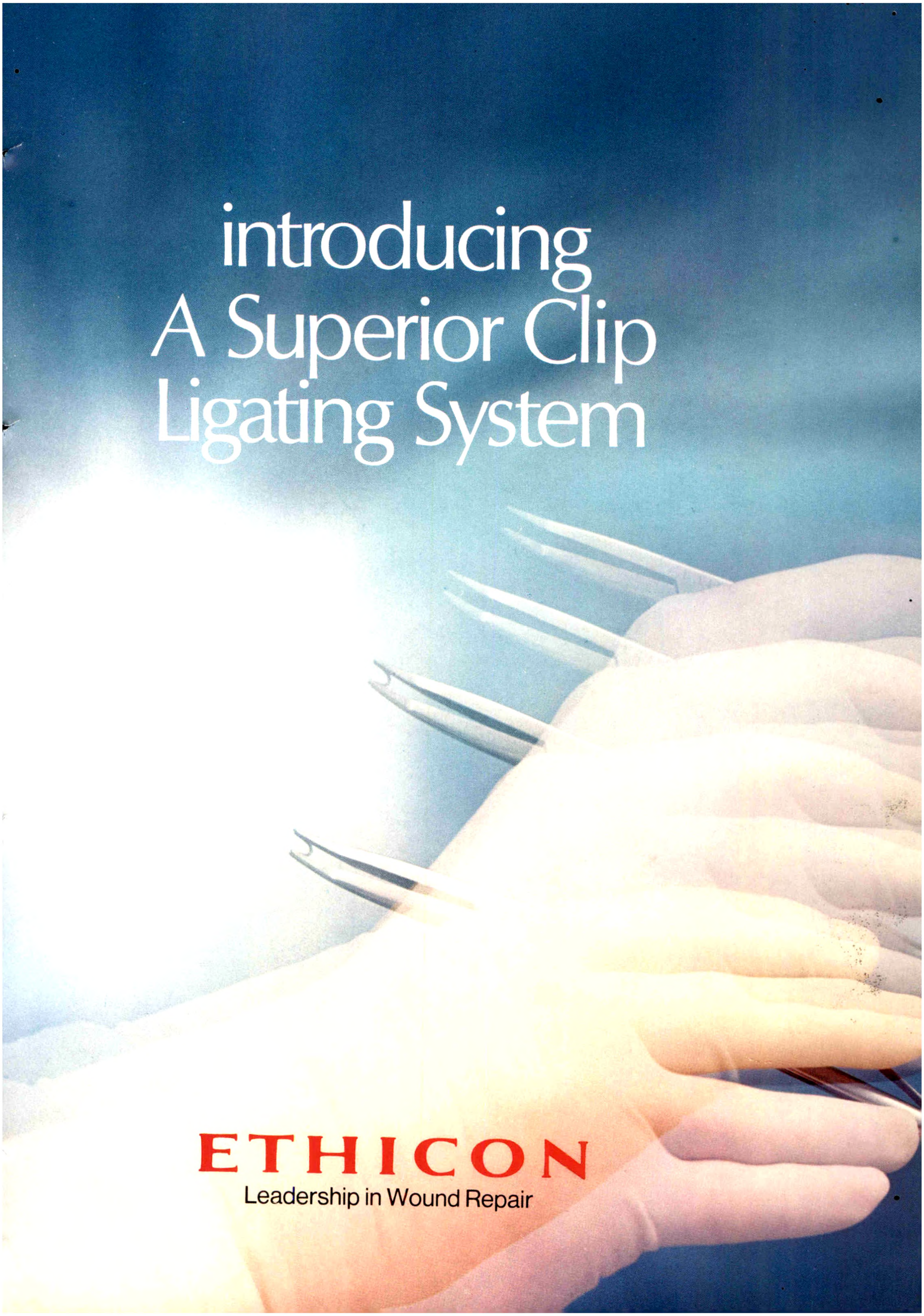
[091372]

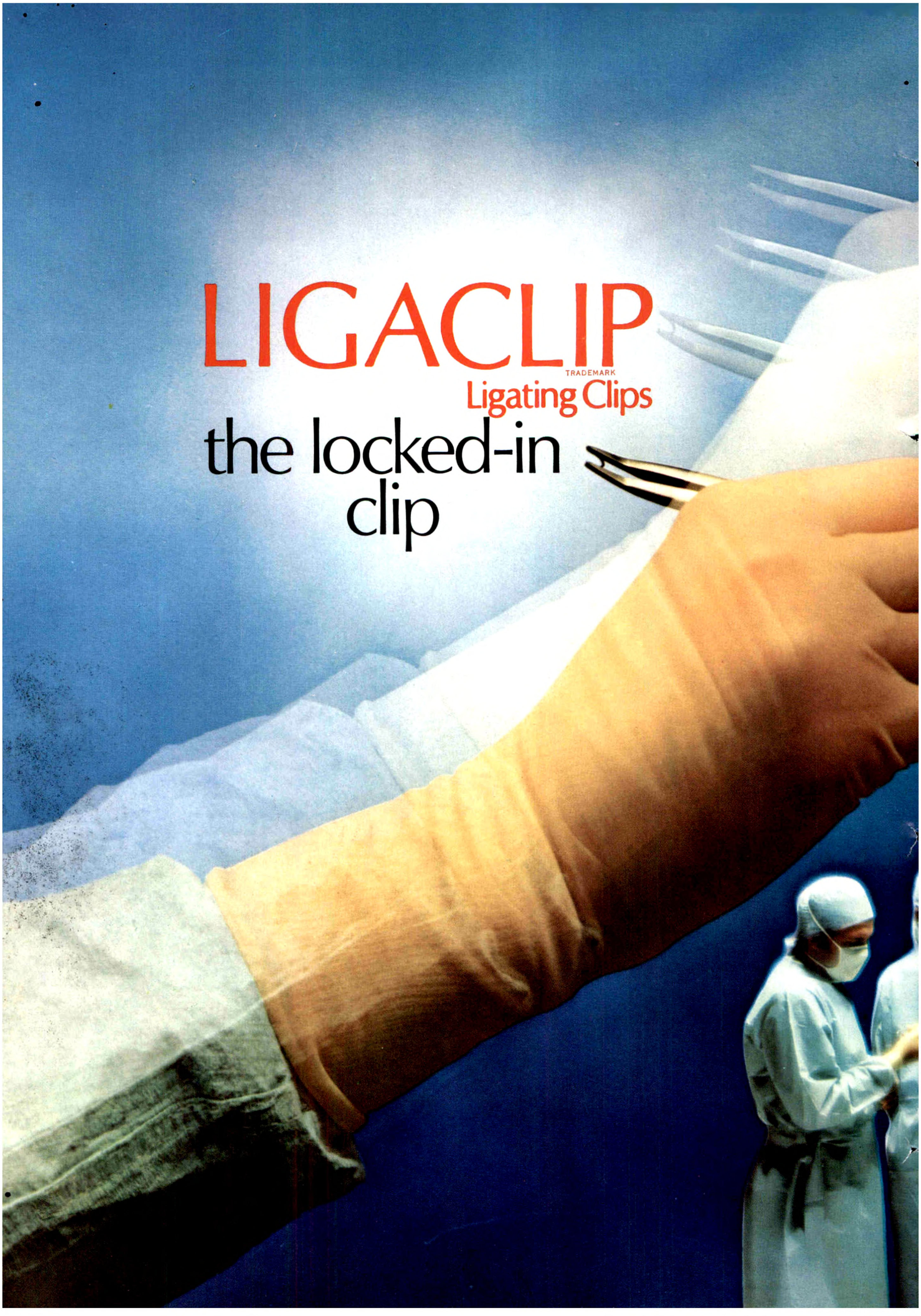
Additional information available to the profession on request.

Eli Lilly and Company, Indianapolis, Indiana 46206

Lilly

200813


introducing
A Superior Clip
Ligating System
ETHICON
Leadership in Wound Repair


LIGACLIP
TRADEMARK
Ligating Clips
the locked-in clip

Why tolerate lost clips, slipped clips, or loose appliers? ETHICON, INC. now offers you the new reliable LIGACLIP Ligating Clips and Appliers. Meticulously crafted appliers grasp the clips and shape them to fit and lock into the applier. Unlike ordinary clips, they're secure from pick-up to closure. Just as ETHICON, INC. offers you LIGAPAK* Ligatures as a superior alternative in suture ligation, this new system sets the standard in clip ligation.

ETHICON

Leadership in Wound Repair

*TRADEMARK

LIGACLIP
TRADEMARK
Ligating Clips

unparalleled security from pick-up to closure

secure transfer
There's no need for you—or the nurse—to maintain tension during transfer since the clip is locked in the applier. Transfer is fast and secure.

accurate placement
The applier and clips are designed to provide accurate alignment. Twisting and slipping are virtually eliminated.

precise distal closure
When you apply pressure, the Tantalum clip forms a precise distal closure. Applier withdrawal is smooth and easy.

ETHICON Leadership in Wound Repair

©ETHICON, INC. 1973 340685

Experimental Esophageal Lye Burns

II. Correcting Established Strictures with Beta-Aminopropionitrile and Bougienage

JOHN W. MADDEN, M.D., WILLIAM M. DAVIS, M.D., COOLEY BUTLER, II, M.D.,
ERLE E. PEACOCK, JR., M.D.

THE SEQUELAE of chemical injury of the esophagus remain a major medical problem.[17] Ingestion of corrosive agents, particularly strong alkalies, may produce acute perforation and death or, more typically, chronic esophageal stenosis and significant morbidity.[21] When initial injury penetrates the entire esophageal wall or subsequent infection converts a deep partial thickness burn into a full thickness injury, free perforation with catastrophic complications may occur. Most burns, however, do not result in free perforation. Partial thickness injuries and, occasionally, even full thickness burns are walled off by surrounding tissues and heal. Although this normal response of esophagus to injury may prevent acute perforation, wound healing and scar formation create additional pathophysiology. During healing, the normally pliant esophagus may be converted into a rigid, narrow tube incapable of passing food. As necrotic tissue sloughs and the resultant ulcer heals, large deposits of dense scar tissue replace the normal submucosal and muscle layers. The presence of scar tissue alone may be of little consequence. However, if scar prevents the esophagus from dilating adequately or narrows the esophagus beyond critical limits, normal deglutition is impossible. Thus, the physical properties and form of esophageal scar tissue determine the physiological outcome of injury.

From the Departments of Surgery and Pathology,
University of Ariona, College of Medicine,
Tucson, Arizona 85724

Standard treatment of lye ingestion is designed to alter form of esophageal scar tissue by mechanical bougienage and to alter inflammatory response and quantity of scar deposited by administering pharmacological doses of steroid hormones. Unfortunately, neither of these therapeutic measures are fully effective.[13] Limited data are available on the biology of visceral wound healing. However, if esophageal and cutaneous wound healing are analogous processes, failure of standard therapy can be explained biologically. Form of surface scars can be altered by mechanical means, but splints must be applied continuously for many months to achieve a permanent correction. In esophageal injuries, bougienage (a form of mechanical splinting) can only be performed intermittently. Each episode corrects rather than prevents form alterations, presumably creating new wounds and more scar. Although steroid hormones reduce acute inflammation, rate of protein synthesis, and rate of scar formation significantly, permanent effects on quantity or quality of scar tissue may not occur. Ultimately, wounds heal under the influence of systemic steroids with the accumulation of large amounts of scar. Systemic steroids change the rate of wound healing but may not alter the

---

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25–27, 1973.

Supported by Grant AM14047, National Institutes of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014.

quantitative aspects of scar formation. In addition, both mechanical bougienage and pharmacological doses of steroids have significant mortality and morbidity. Because of these inherent failings of current therapy, we have investigated new approaches to the prevention and therapy of esophageal stenosis.

The physical characteristics of all mesenchymal tissues including scars are directly related to the physical properties of collagen fibers. Therefore, altering quantity or physical properties of scar collagen should alter the pathophysiology of esophageal injury. In order to be useful clinically, anticollagenous agents must specifically affect collagen without interfering with metabolism of other biologically important molecules and selectively affect collagen in pathological lesions without influencing structural integrity of normal mesenchymal tissues.[18] Selectivity can be achieved by using agents affecting only newly synthesized collagen in situations where collagen is turning over more rapidly in diseased than in normal tissues. Specificity can be achieved either by inhibiting unique steps in collagen maturation or by interfering specifically with collagen synthesis. Although several methods of inhibiting collagen synthesis are under study, none appear to be ready for clinical trial in the near future. Normal collagen maturation, however, can be inhibited specifically in animals and man using agents currently undergoing clinical evaluation.

The physical properties of newly synthesized scar tissue depend upon the amount of collagen synthesized, the physical weave of the collagen fibers, and the number of covalent bonds between collagen molecules. Although several types of cross bonds have been identified, covalent bonds derived from aldehyde precursors are the major stabilizing force in fiber formation.[25] Covalent bonding in newly synthesized collagen can be prevented specifically by a class of chemical compounds called lathyrogens. Beta-aminopropionitrile (BAPN), the most powerful known osteolathyrogen, specifically inhibits the action of lysyl oxidase and prevents the oxidative deamination of lysyl residues in collagen.[27] Because lysine derived aldehydes are necessary for the production of normal covalent bonds between molecules, collagen synthesized under the influence of BAPN fails to form covalent cross bonds. Lathyritic collagen forms fibers morphologically indistinguishable from normal collagen; lathyritic fibers, however, have significantly decreased tensile strength.[28] The systemic administration of BAPN in doses insufficient to produce generalized mesenchymal effects, reduces burst strength of healing skin wounds in rats, reduces the restrictive effect of adhesions around flexor tendon repairs in chicken's feet, and changes the type and amount of scar tissue in dimethylnitrosamine-induced hepatic cirrhosis in rats.[4,9,23] In addition, BAPN specifically inhibits covalent cross bonding in newly synthesized collagen in man.[14,24]

Recently, we have demonstrated that inhibiting lysyl oxidase activity prevents stenosis in dogs with acute esophageal lye burns.[5] BAPN alone, without addition of mechanical bougienage, is as effective in preventing esophageal stenosis as large doses of systemic steroid hormones and bi-weekly bougienage. The following studies were performed to test the hypothesis that inhibiting intermolecular covalent bonding in newly synthesized scar collagen with the addition of mechanical bougienage can reverse established esophageal stenosis.

Materials and Methods

The canine model of esophageal stenosis used in these studies has been described elsewhere.[5] Under Nembutal anesthesia, the distal esophagus was exposed through a left thoracotomy incision. Great care was taken not to disturb the longitudinal and segmental blood supply. A double lumen, plastic nasogastric tube inserted through the mouth was isolated within a 5 cm. esophageal segment with umbilical tapes. A 20% solution of sodium hydroxide was instilled into the isolated segment until a pressure of 30 cms. of water could be measured. After maintaining the pressure for 60 seconds, the sodium hydroxide was removed and the isolated segment irrigated with distilled water for 15 seconds at a pressure of 30 cm. of water. Washing was repeated three times. Before the chokers were removed, extent of the burn was marked with stainless steel wire sutures placed in the muscle and the submucosal layers at either end of the burned segment. Distance between sutures was measured carefully while the chest was open and by X-ray after the thoracotomy was closed.

Barium esophagograms were performed prior to burning and every 2 weeks throughout the experiment. Under general anesthesia, animals were positioned a standard distance from X-ray source and film cassette. Thin barium was introduced into the upper esophagus through a plastic catheter at a pressure of 30 cm. of barium-water mixture. Exposures were made when barium regurgitated into the mouth or when 500 ml. had been administered. The process was repeated twice. Esophageal diameter was determined by measuring the narrowest portion of the barium column between the wire sutures on both exposures and determining the mean.

At sacrifice, the esophagus was inflated with 10% neutral buffered formalin after ligating proximal and distal ends beyond the injured segment and was immersed for at least 48 hours in the same fluid. Longitudinal and transverse transmural blocks were excised from the injured segment and examined histologically. Where the injury appeared eccentric, the area of maximum destruction was included in the longitudinal block.

Experimental Design

Forty adult mongrel dogs had standard esophageal lye burns as described. All were fed a soft solid diet for 4 weeks and had no other treatment. During this interval, four dogs died of acute esophageal perforation. At 4 weeks, barium esophagograms were analyzed and the 30 animals with the smallest esophgeal diameters were randomly divided into three groups. Group I received no therapy and served as controls for Groups II and III. Group II were begun on daily injections of Prednisolone (0.1 mg./Kg.). Group III received BAPN fumarate (100 mg. base/Kg.) as daily intraperitoneal injection. Previous data indicate that this dose of BAPN inhibits covalent bonding in newly synthesized collagen significantly without producing measurable effects on mature connective tissue.[5] In addition to daily drug injections, Groups II and III were dilated weekly under general anesthesia with a tapered 46 French mercury filled esophageal bougie (Maloney type). Groups II and III were treated for 6 weeks, beginning 4 weeks after the esophageal burn, and followed for an additional 20 weeks after the cessation of therapy (Fig. 1).

Our previous experience with this canine model demonstrated that only deep, muscle penetrating burns produced permanent esophageal stricture.[1] Therefore, at the conclusion of the experiment, each esophageal specimen was examined and the depth of burn established. The examiners had no knowledge of the previous treatment administered. Only animals with deep, penetrating muscle burns will be considered. Two of the controls, three of the steroid treatment group, and two of the BAPN group had superficial burns and were discarded.

Results

Mean esophageal diameters for all groups are presented in Table 1. During the 4 weeks prior to treatment, all animals lost weight and developed significant esophageal stenosis by esophagogram. At the beginning of treatment, esophageal diameters were comparable in all groups. During the 6-week treatment interval, mean esophageal diameters of the steroid plus bougienage group increased slightly but did not differ significantly from the control group. No further increase in mean esophageal diameter occurred during the 5-month follow-up period (Fig. 2). In contrast, the mean esophageal diameters of the BAPN plus bougienage group increased steadily during treatment. By the end of the treatment interval, mean esophageal diameter was significantly larger than both the steroid plus bougienage and control groups ($p < 0.02$). After treatment was discontinued, mean esophageal diameter continued to increase, reaching a maximum at 18 weeks, and remaining constant thereafter throughout the remainder of the 7-month observation period (Fig. 2).

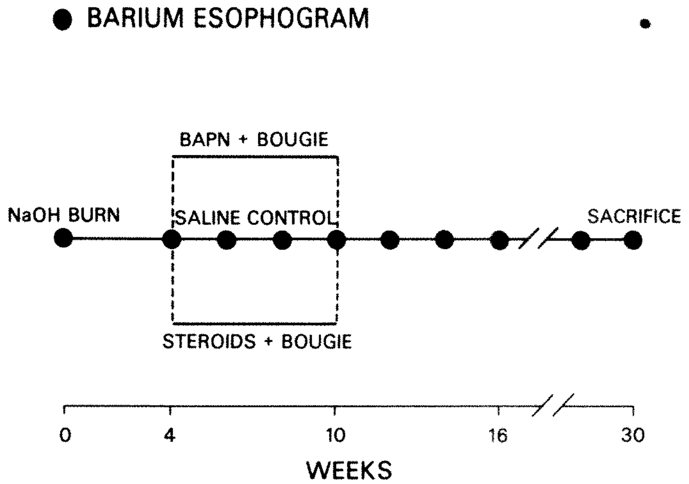


Fig. 1. Experimental design. At 30 weeks, dogs were sacrificed and only animals with deep muscle penetrating burns were considered.

Clinically, dogs in the three groups behaved differently. By the fourth week, despite ravenous appetites, all animals had difficulty swallowing a soft solid diet. Food swallowed quickly would be regurgitated a few moments later. After many attempts, however, some food would pass into the stomach. Control animals

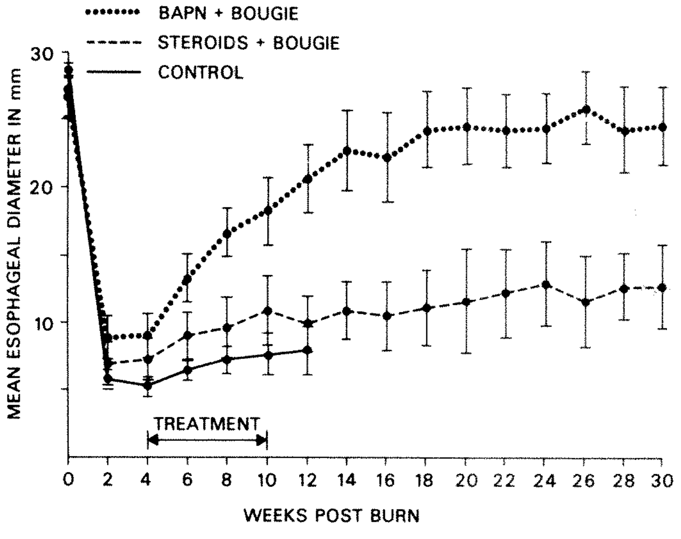


Fig. 2. Mean esophageal diameters and standard errors for the three groups. Although dogs were treated from the 4th through the 10th weeks, BAPN animals continued to improve for an additional 8 weeks.

TABLE 1. *Smallest Diameter of Esophagus*
(mean, mm ± SE)

	Group I Control (n=8)	Group II Steroids + Bougienage (n=7)	Group III BAPN + Bougienage (n=8)
Pre-burn	28.5 ± 0.6	27.2 ± 2.1	26.7 ± 1.5
2 Weeks	6.1 ± 0.8	7.0 ± 1.5	8.8 ± 1.5
4 Weeks	6.8 ± 0.8	7.3 ± 1.6	7.9 ± 1.6
6 Weeks†	6.5 ± 0.8	9.0 ± 1.8	13.3 ± 1.7
8 Weeks	7.3 ± 1.0	9.7 ± 2.3	16.7 ± 1.8
10 Weeks	7.7 ± 1.6	11.0 ± 2.5	18.3 ± 2.2*
12 Weeks	8.0 ± 1.8	10.0 ± 2.0	20.7 ± 2.3*
14 Weeks		11.0 ± 2.1	22.8 ± 2.7*
16 Weeks		10.6 ± 2.5	22.3 ± 2.1*
18 Weeks		11.2 ± 2.7	24.3 ± 2.6*
20 Weeks		11.7 ± 3.8	24.6 ± 2.6*
22 Weeks		12.3 ± 3.2	24.3 ± 2.5*
24 Weeks		13.0 ± 3.1	24.5 ± 2.4*
26 Weeks		11.7 ± 3.3	26.0 ± 2.5*
28 Weeks		12.8 ± 2.4	24.4 ± 3.0*
30 Weeks		12.8 ± 3.0	24.7 ± 2.7*

† Animals treated from Week 4 through Week 10
* Significantly greater than Groups I and II, $p < 0.02$

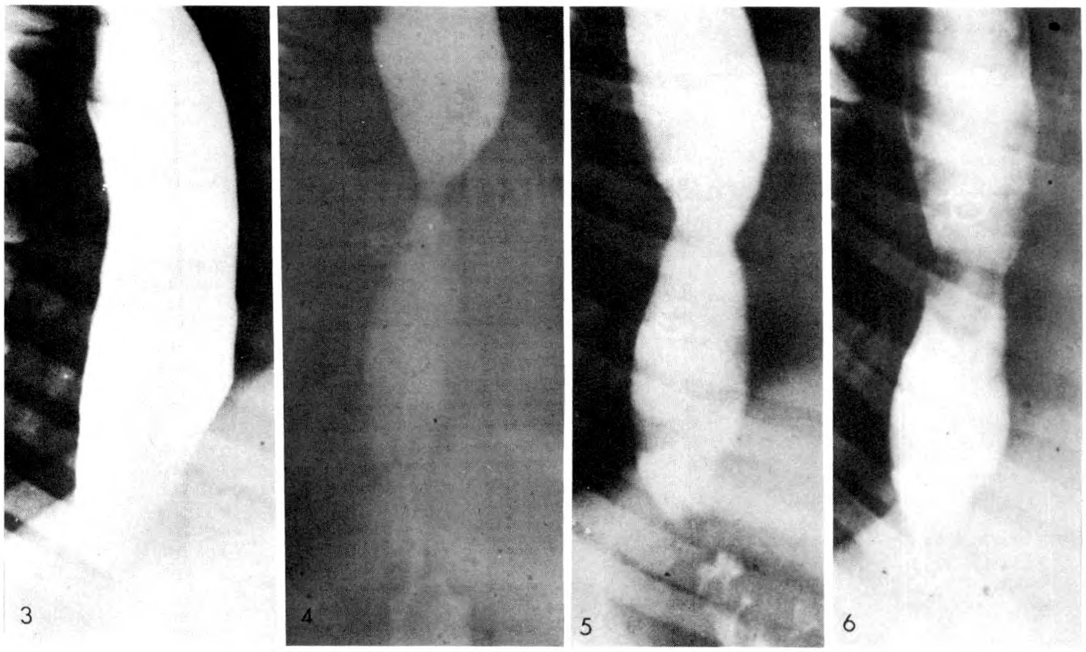
maintained this behavior until weight loss was significant or they lost interest in eating. By the 12th week, the majority of control animals had reached this state and were sacrificed. With the exception of one animal, the steroid plus bougienage group improved with the onset of therapy. Although all steroid plus bougienage animals continued to regurgitate, some food could be swallowed after several attempts. By the end of the 6-week treatment interval, steroid plus bougienage dogs continued to regurgitate, but maintained their weight. The lone exception could not maintain weight despite steroid plus bougienage treatment and was sacrificed in the sixth week of treatment; esophageal diameter during the final week was less than 4 mm. In contrast, BAPN plus bougienage treated animals improved steadily with the onset of therapy. (Figs. 3–6) By 6 weeks, all animals ate without regurgitating and maintained or increased their weight during the observation period.

Histologic examination of the esophagi at the conclusion of the experiment revealed that submucosa and muscle layers of all animals had been replaced by dense scar tissue. Examination of specimens without prior knowledge of treatment failed to reveal significant histological differences. Although thickness of regenerated epithelium and vascularity of scar varied slightly, differences observed within each group were greater than differences between groups. (Figs. 7–8) Even in retrospect, BAPN treated animals could not be distinguished from steroid treated dogs. No histologic abnormalities of collagen fibers were observed under the light microscope and the size and type of scar, estimated in Masson trichrome stained preparations, seemed the same in all groups. Two of the BAPN treated animals, however, developed generalized transmural thinning of the esophagus. Both animals had full thickness burns completely healed without stricture.

Discussion

Although methods of preventing esophageal stenosis following acute lye burns have been investigated extensively in animals and man, technics for correcting established strictures have received minimal study. In acute burns, steroids alone, BAPN alone, or steroids plus bougienage reduce stricture formation significantly.[5,7,15] Bougienage alone, however, does not prevent the development of esophageal stenosis.[8,15] Nevertheless, despite the inadequacies of bougienage, clinicians must rely on chronic mechanical dilatation once a fibrous stricture is established. If the esophagus receives a superficial injury and strictures are mild, bougienage provides lasting benefits. However, in severe penetrating injuries with extensive scarring and tight strictures, bougienage fails frequently.[6] Even with the addition of local steroid injections, chronic bougienage may not provide an adequate passage for food.[12]

In our canine model, dilating established strictures with the addition of systemic steroids failed to provide normal esophageal size or to restore normal eating patterns. Following each dilatation, steroid treated dogs seemed to swallow a soft solid diet more easily and to regurgitate less frequently. Improvement, however, was temporary. Within a few days, swallowing problems recurred. Mean esophageal diameters of the steroid plus bougienage group were slightly larger than the controls. Although statistically insignificant, this



FIGS. 3–6. Barium esophagograms of the dog who responded *least well* to BAPN therapy. (3) Prior to burning. (4) At 4 weeks, just prior to beginning treatment. (5) After 6 weeks of BAPN and bougienage treatment. Esophageal diameter is 3 times the pretreatment measurement. (6) After seven months of observation. Esophageal diameter is 4 times the pretreatment measurement. Despite the mild stenosis, the dog ate normally.

small difference may account for improved clinical behavior.

In contrast, BAPN plus mechanical bougienage reversed established esophageal stenosis, restoring normal esophageal patency and adequate physiological function. More important, once stenosis had been corrected, strictures did not recur in BAPN treated dogs. By the end of the treatment interval, animals ate without regurgitation and, by 18 weeks, feeding patterns in all dogs seemed entirely normal.

Because of our limited knowledge of how visceral wounds heal and how mechanical dilatation affects morphology and kinetic chemistry of scars, the mechanism by which lysyl oxidase inhibition plus bougienage reverses fibrous stricture is not clear. Data available from studies of cutaneous wound healing, however, provide at least two hypotheses. Despite their histologic appearance, dermal wounds remain metabolically active for prolonged periods.[20] New scar collagen is deposited and older material is removed at a rapid rate for many months. If the metabolic turnover of esophageal scar collagen remains elevated during the period of BAPN administration, newly deposited collagen would be lathyritic. Because lathyritic collagen lacks the great tensile strength of normally cross bonded fibers, mechanical dilatation could cause slippage of individual fiber bundles or rupture of non-covalent intermolecular bonds without creating a physical discontinuity in the scar. This hypothesis suggests that as esophageal scar collagen undergoes rapid metabolic turnover in the presence of a lysyl oxidase inhibitor, rigid esophageal scar becomes pliant and mechanical dilatation stretches the scar without creating new wounds. However, if rate of collagen turnover is not rapid enough to produce a lathyritic scar quickly, bougienage could rupture the stenotic segment creating a new esophageal wound. As the wound heals under the influence of BAPN, newly deposited collagen would be lathyritic. Subsequent mechanical dilatation could stretch or slip lathyritic fibers maintaining esophageal size without additional injury. Data from acute esophageal lye burn experiments suggest that in the presence of lathyritic scars even swallowing a soft solid diet dilates the esophagus and maintains patency.[5] In addition, although lathyrism has no affect on the contraction of cutaneous wounds, careful examination of esophagi from acute experiments indicates that lysyl oxidase inhibition may prevent wound contraction following esophageal injury.[2] Thus, a second hypothesis suggests that dilating a fixed fibrous stricture creates new wounds and, under the influence of BAPN, new scar formed remains pliable and easily stretched.

Both of these hypotheses are testable and point out the urgent need for careful study of biochemistry and mechanics of visceral wound healing. Preliminary experiments have demonstrated that visceral and cutaneous wounds differ significantly in rate of strength gain and in biochemical kinetics.[11] Currently, there are no quantitative data on visceral wound contraction.

Esophageal architecture differs from species to species. Several authors have stressed the differences between canine and human esophageal anatomy and physiology.[8] The canine model used in these experiments does not represent human esophageal stenosis. Our data demonstrate, however, that fibrous esopha-

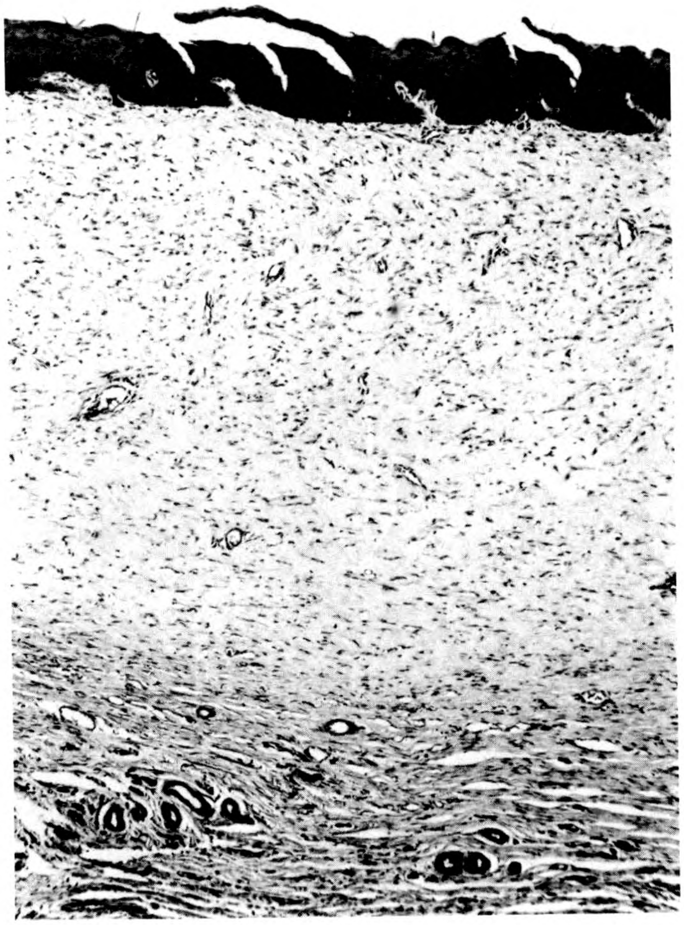


FIG. 7. Photomicrograph of esophagus from a steroid plus bougienage-treated dog 30 weeks post-burning. Dense scar tissue has replaced the entire esophageal wall including the muscularis. (Mallory's Trichrome, 105x magnification)

geal strictures created in the dog using these technics are stable over long time intervals and produce permanent physiological impairment.[1] Occasionally, we have noted a discrepancy between the functional diameter of the esophagus as measured by standard barium esophagograms and esophageal diameter measured in fixed postmortem specimens. Because of our interest in the effects of treatment on pathophysiology, we have stressed the functional rather than the fixed anatomical measurements.

Transmural thinning of the esophagus noted in two of our BAPN treated dogs is curious. This phenomenon, although unexplained, is not limited to BAPN treated animals. Control dogs, without treatment of any kind, have developed transmural thinning as early as 4 weeks following burning.[2] In addition, Rosenberg *et al,* noted esophageal thinning in rabbits treated with steroids following esophageal lye burns.[26] Generalized thinning may be due to rapid tissue remodeling secondary to the burn itself and deserves further study.

Data presented in this paper establish the principle that pathophysiology created by inappropriate fibrous tissue deposition can be altered significantly by interfering with normal scar collagen metabolsim. BAPN is only one example of several anticollagenous agents with clinical potential. Inhibiting collagen synthesis, either by chelating metals functioning as cofactors for proline hydroxylation or by introducing proline analogues incapable of hydroxylation, is an attractive area for study. Unfortunately, data on the *in vivo* effects of these agents are contradictory.[3,16,19,29] As yet, data demonstrating significant effects on wound healing by specifically inhibiting collagen synthesis *in vivo* are not available. Currently, agents specifically interfering with normal collagen maturation seem to be the most promising. In addition to BAPN and other lysyl oxidase inhibitors, d-penicillamine, an agent chelating lysine-derived aldehydes, produces lathyrism in animals and

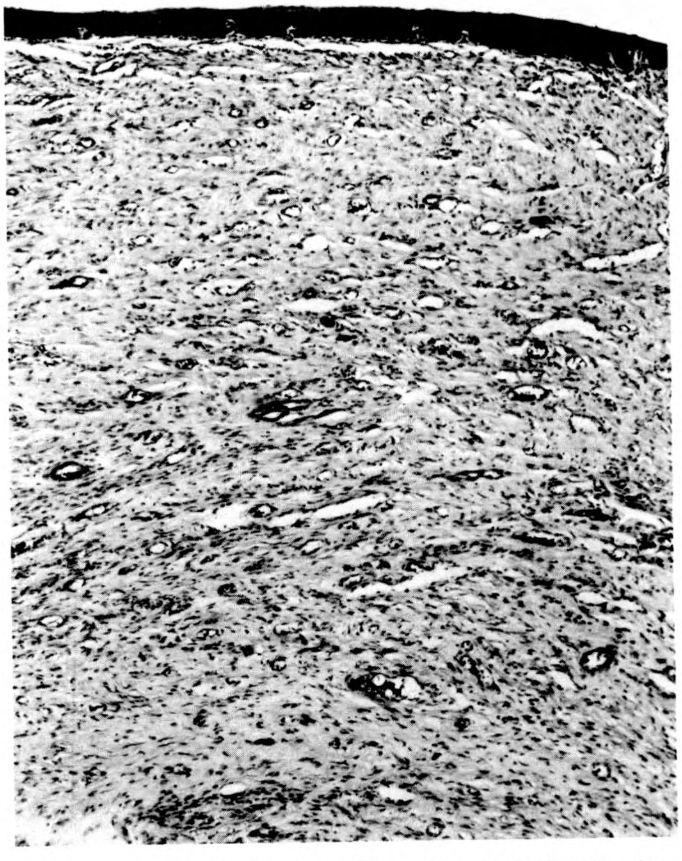


FIG. 8. Photomicrograph of esophagus from a BAPN plus bougienage-treated dog 30 weeks post-burning. The dense scar tissue replacing the entire wall is more vascular and slightly more cellular than specimen shown in Figure 7. Differences of even greater magnitude, however, occurred within groups. (Mallory's Trichrome, 105x magnification)

man.[10,22] Because of the potential clinical usefulness of these agents, further study in man seems warranted. Under FDA supervision, double-blind controlled studies of the effects of BAPN and d-penicillamine on pathophysiology of human diseases are in progress.

Summary

1. Instillation of 20% sodium hydroxide under carefully controlled conditions creates a standard injury of the mucosal, submucosal, and muscular layers of the canine esophagus. Healing, over a 4-week period, produces a fixed, fibrous stricture which results in severe dysphagia and significant inanition.

2. Treating 4-week old established strictures for 6 weeks with weekly bougienage and daily administration of Prednisolone improved the ability of dogs to swallow, but did not produce a significant increase in esophageal diameter nor restore normal eating patterns. After discontinuing therapy, neither clinical behavior nor esophageal diameters improved during a 20-week post-treatment observation period.

3. Treating 4-week old fibrous strictures for 6 weeks with weekly bougienage and daily administration of BAPN (a powerful lysyl oxidase inhibitor) produced a significant increase in esophageal diameter ($p < 0.02$) and restored normal deglutition. After discontinuing therapy, both the nutritional status of the animals and esophageal diameters continued to improve during a 20-week post-treatment observation period.

4. BAPN inhibits the formation of intermolecular covalent bonds in newly synthesized collagen. Substitution of collagen with a low cross bonding density for normal collagen in metabolically active scar tissue may be responsible for the significant differences in esophageal diameter and clinical behavior observed between steroid and BAPN groups.

References

1. Butler, C. II, Madden, J. W., Davis, W. M. and Peacock, E. E., Jr.: Morphologic Aspects of Experimental Esophageal Lye Stricture: 1. Pathogenesis and Pathophysiologic Correlations. Proc. Soc. Exper. Bio. Med. (in press).
2. Butler, C. II, Madden, J. W., Davis, W. M. and Peacock, E. E., Jr.: Morphologic Aspects of Experimental Esophageal Lye Stricture: 2. Effects of Steroid Hormones, Bougienage and Induced Lathyrisim on Acute Lye Burns. Proc. Soc. Exper. Biol. Med. (in press).
3. Chvapil, M., Madden, J. W., Carlson, E. C. and Peacock, E. E., Jr.: Effects of cis-Hydroxyproline on Collagen and Other Metabolites in Skin Wounds, Granuloma Tissue, and Liver of Mice and Rats. (in press).
4. Craver, J. M., Madden, J. W. and Peacock, E. E., Jr.: Biological Control of Physical Properties of Tendon Adhesions. Effect of Beta-aminopropionitrile in Chickens. Ann. Surg., 167:697, 1968.
5. Davis, W. M., Madden, J. W. and Peacock, E. E., Jr.: A New Approach to the Control of Esophageal Stenosis. Ann. Surg., 176:469, 1972.
6. Fatti, L., Marchand, P. and Crawshaw, G. R.: The Treatment of Caustic Strictures of the Esophagus. Surg. Obstet. Gynecol., 102:195, 1956.
7. Haller, J. A., Jr., Andrews, H. G., White, J. J., Tamer, M. A. and Cleveland, W. W.: Pathophysiology and Management of Acute Corrosive Burns of the Esophagus: Results of Treatment in 285 Children. J. Ped. Surg., 6:578, 1971.
8. Haller, J. A., Jr. and Bachman, B. A.: The Comparative Effect of Current Therapy on Experimental Caustic Burns of the Esophagus. Pediatrics, 34:236, 1964.
9. Haney, A., Peacock, E. E., Jr., Madden, J. W.: Liver Regeneration and Hepatic Collagen Deposition in Rats With Dimethylnitrosamine–Induced Cirrhosis. Ann. Surg., 175: 863, 1972.
10. Harris, E. D., Jr. and Sjoerdsma, A.: Effect of Penicillamine on Human Collagen and its Possible Application to Treatment of Scleroderma. Lancet, ii:996, 1966.
11. Hastings, J. C. and Van Winkle, W., Jr.: Organ Differences in Post-operative Healing. Surg. Forum, 23:29, 1972.
12. Holder, T. M., Ashcraft, K. W. and Leape, L.: The Treatment of Patients with Esophageal Strictures by Local Steroid Injections. J. Ped. Surg., 4:646, 1969.
13. Imre, J. and Kopp, M.: Arguments Against Long-term Conservative Treatment of Oesophageal Strictures Due to Corrosive Burns. Thorax, 27:594, 1972.
14. Keiser, H. and Sjoerdsma, A.: Studies on Beta-aminopropionitrile in Patients with Scleroderma. Clin. Pharmacol. Ther., 8:593, 1967.
15. Knox, W. G., Scott, J. R., Zintel, H. A., Guthrie, R. and McCabe, R. E.: Bougienage and Steroids Used Singly or in Combination in Experimental Corrosive Esophagitis. Ann. Surg., 166:930, 1967.
16. Lane, J. M., Bora, F. W., Jr., Prockop, D. J., Heppenstall, R. B. and Black, J.: Inhibition of Scar Formation by the Proline Analog cis-Hydroxyproline. J. Surg. Res., 135: 137, 1972.
17. Leape, L. L., Ashcraft, K. W., Scarpelli, D. G., Holder, T. M.: Hazard to Health-Liquid Lye. N. Engl. J. Med., 284:578, 1971.
18. Madden, J. W.: Wound Healing: Biologic and Clinical Features, a chapter *in* Christophers Textbook of Surgery, Sabiston, D. ed., Philadelphia, Saunders, 1972.
19. Madden, J. W., Chvapil, M., Carlson, E. C. and Ryan, J. N.: Toxicity and Metabolic Effects of 3,4–Dehydroproline in Mice. Toxical. Appl. Pharmacol. (in press).
20. Madden, J. W. and Peacock, E. E., Jr.: Studies on the Biology of Collagen During Wound Healing, III. Dynamic Metabolism of Scar Collagen and Remodeling of Dermal Wounds. Ann. Surg., 174:511, 1971.
21. Marchand, P.: Caustic Strictures of the Oesophagus. Thorax, 10:171, 1955.
22. Nimni, M. E., Deshmukh, K., Gerth, N. and Bavetta, L. A.: Changes in Collagen Metabolism Associated with the Administration of Penicillamine and Various Amino and Thiol Compounds. Biochem. Pharmacol., 18:707, 1969.
23. Peacock, E. E., Jr. and Madden, J. W.: Some Studies on the Effect of Beta-aminopropionitrile on Collagen in Healing Wounds. Surgery, 60:7, 1966.
24. Peacock, E. E., Jr. and Madden, J. W.: Some Studies on the Effects of Beta-aminopropionitrile in Patients with Injured Flexor Tendons. Surgery, 66:215, 1969.
25. Piez, K. A.: Cross Linking of Collagen and Elastin. Ann. Review Biochem., 36:547, 1968.
26. Rosenberg, N., Kunderman, P. J., Vroman, L. and Moolten, S. E.: Prevention of Experimental Lye Strictures of the

Esophagus by Cortisone. Arch. Surg., 63:147, 1951.

27. Siegel, R. C., Pinnell, S. R., Martin, G. R.: Cross-Linking of Collagen and Elastin. Properties of Lysyl Oxidase. Biochem., 9:4486, 1970.

28. Tanzer, M. L. and Gross, J.: Collagen Metabolism in the Normal and Lathyritic Chick. J. Exper. Med., 119:275, 1964.

29. Whitson, T. C. and Peacock, E. E., Jr.: Effect of Alpha Alpha Dipyridyl on Collagen Synthesis in Healing Wounds. Surg. Gynec. Obstet., 128:1061, 1969.

DISCUSSION

DR. HARRY H. LEVEEN (Brooklyn): The results presented by the authors do confirm the value of lathrogenic drugs in the treatment of disabling strictures of the esophagus.

A year ago when a similar paper was presented to the society on this topic, I asked the authors why they had chosen BAPN rather than B-penicillamine. By this I meant to suggest that penicillamine would be a better choice than BAPN. At this time again I would like to put forth the suggestion with greater force.

We, like many others, have been studying the effects of penicillamine on collagen synthesis, especially in wound healing. Penicillamine has the advantage that it has already been used in humans, mainly for Wilson's disease, rheumatoid arthritis and cystine stones, but it has also been used in human diseases characterized by excessive fibrosis. Some patients have been treated with penicillamine for 5 or 10 years without adverse effects. Adverse effects which do occur are known and reversible. Penicillamine increases soluble collagen in tissues at the expense of insoluble collagen. BAPN is much less active in this regard. Dasler in 1961 showed that BAPN reduced the percentage of insoluble collagen and increased the percentage of soluble collagen in subcutaneously implanted vinyl sponges. (Metabolism 110:883, 1961) Nimni and Bavetta repeated this work using penicillamine instead of BAPN, the results were far greater than had been observed with BAPN. (Science 150:905, 1965) In Copenhagen, a surgeon has used penicillamine clinically to prevent keloid formation in susceptible patients. Because penicillamine therapy increases soluble collagen at the expense of insoluble collagen, Harris has even suggested its use in scleroderma, a disease where esophageal stenosis is often observed. Penicillamine has been suggested for use in cirrhosis and pulmonary fibrosis. Penicillamine would be more effective in the treatment of esophageal stricture and because so much more is known about its use, it could be used in human cases directly without further animal experimentation.

DR. STANLEY M. LEVENSON (Bronx): I would just like to comment on a point that Dr. Madden raised concerning a possible mechanism underlining the finding he has just reported and to recall to you that this really should come as no surprise to any of us.

Lind, more than 200 years ago, reported that when sailors become scorbutic, wounds they had received years before and had long since healed broke down without further trauma, the inference being of course that the wound was still an active, dynamic part of the body quite different from the ordinary uninjured connective tissue, even after many years.

Experimentally, that fact was confirmed in the laboratory about 25 or 30 years ago by a type of experiment analogous to Dr. Madden's. Laparatomy wounds were made in guinea pigs which were maintained on a normal intake of ascorbic acid (Proc. Soc. Exptl. Biol. Med. 82:95, 1953). After about 6 weeks the guinea pigs were placed on a vitamin C deficient diet. The laparatomy wounds, which had healed normally for the first 6 weeks weakened and some became hernias; microscopically one could see the collagen had disappeared.

I think what is happening in Dr. Madden's study is that when BAPN is begun 1 month after the insult, the scar tissue is turning over very dynamically, as Dr. Madden indicated when he said "this fresh scar tissue." As the collagen is reabsorbed, new collagen is laid down which is now under the influence of the BAPN. Now we have a situation which is analogous to that which Madden and Peacock reported last year, namely, that as collagen is laid down the BAPN will interfere with its cross-linking.

This is a very important observation and I would agree that it does have potential for many situations; materials such as penicillamine or other cross-linking inhibitors less toxic than BAPN may prove even more useful.

DR. J. W. MADDEN (Closing): As far as Dr. LeVeen's specific questions are concerned, we have two double-blind controlled experiments in progress designed to see whether we can influence the patho-physiology of fibrotic disease in man using d-penicillamine.

The problem with using d-penicillamine in experimental animals is its expense. If we can demonstrate an effect with BAPN, experiments with d-penicillamine are then justified.

Currently, we are using d-penicillamine in an attempt to reverse chronic esophageal stenosis in this canine model.

The second point Dr. LeVeen made concerned the use of d-penicillamine in scleroderma. I believe he may have misinterpreted Harris's paper. Actually, there have been three other publications since Harris' initial work on d-penicillamine in scleroderma and most of them have indicated, in fact all of them indicate, that d-penicillamine has no usefulness in scleroderma.

There are specific criteria one can set down that human diseases must meet before anti-collagenous agents could be considered and scleroderma does not fit them.

As far as the increase in saline extractable collagen that d-penicillamine produces, d-penicillamine does seem to take apart Shiffs-base bonds, (the acid soluble collagen bonds) where BAPN does not.

Our experience with d-penicillamine in man indicates that in the doses the FDA allows us to give, it is a much less effective lathrogenic agent than BAPN

As far as Dr. Levenson's questions are concerned, we discuss in the manuscript in some detail the various biological possibilities of how BAPN might work.

Rapid turnover of scar collagen in the esophagus is one possibility, but Dr. Levenson, there is another equal possibility. If scar collagen does not turn over rapidly in the esophagus, then the initial bougienage could rupture the esophageal scar and create a new wound. Then you have rapid collagen synthesis directly under the influence of a lathrogenic agent. The new collagen synthesized would be very weak and have very little tensile strength. I believe that answers both questions.

Divergent Nature of Gastric Mucosal Permeability and Gastric Acid Secretion in Sick Patients with General Surgical and Neurosurgical Disease

MICHAEL J. GORDON, M.D., JOHN J. SKILLMAN, M.D., NICHOLAS T. ZERVAS, M.D., WILLIAM SILEN, M.D.

From the Department of Surgery, Harvard Medical School and the Beth Israel Hospital, Boston, Massachusetts 02215

Acute gastrointestinal ulceration may occur with a variety of systemic conditions such as trauma,[17,18,22] operation,[3,19,27] central nervous system disease,[10] burns,[9,32] hypotension, sepsis, respiratory failure, uremia and jaundice.[16,33] Although acute ulcerations which develop in all of these conditions are commonly grouped together as *stress ulcers*, many features of these ulcers suggest a varied pathogenesis.[35,36]

Davenport[11–14] has shown that damage to canine gastric mucosa induced by a variety of chemical agents results in increased lumen to mucosa back diffusion of hydrogen ions. Many critically ill patients and patients with diseases of the stomach have similarly been found to have greatly increased gastric mucosal permeability to hydrogen ion.[5,30,34]

Estimation of changes in gastric mucosal permeability by the use of technics which employ strongly acid solutions may cause serious bleeding.[38] The fluxes of lithium ion and hydrogen ion from lumen to mucosa are constantly related, not only in the normal stomach, but also when gastric mucosal permeability has been increased by agents which attack the gastric mucosal barrier.[6,7] If one employs a solution of lithium and polyethylene glycol (PEG), a volume marker, alterations in gastric mucosal permeability can be estimated by changes in the lithium to PEG ratio.[37] This technic eliminates the necessity for making complicated corrected flux calculations previously used to assess permeability to hydrogen ion[30,31,34] and is also safer because the necessity to use any hydrogen ion in the test solution is obviated.[20,21]

Gastric mucosal permeability and gastric acid secretion were investigated in 13 patients with general surgical problems and nine patients with neurological disease by the acid-free lithium technic. The purpose of the study was to examine possible differences in these two groups of patients from which one might develop insight into the pathogenesis of Cushing's ulcer of neurosurgical disease and the acute stress ulcer of general surgical disease.

Methods

Twenty-five studies of gastric mucosal permeability (GMP) were performed by the acid-free technic in 22 patients cared for in a Respiratory-Surgical Intensive Care Unit. Nine of the 22 patients (11 studies) had central nervous system. Of the remaining 13 patients, 12 had abdominal operations and one patient had severe viral pneumonia and tension peneumothorax. The latter 13 general surgical patients were divided into two groups based on whether their GMP was normal or increased.

Studies were performed after at least a 10-hour period of fasting. The nasogastric tube was positioned in the stomach to allow free flow and recovery of instilled solutions. Gastric contents were aspirated and the

---

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25–27, 1973.

Supported by U.S.P.H.S. grant #AM 15681 and by a grant from the John A. Hartford Foundation.

Request reprints: John J. Skillman, M.D. at above address.

stomach was washed by instillation and withdrawal of 225 ml. of an isosmotic sodium chloride-lithium chloride test solution, containing 150 mM NaCl, 5 mM LiCl, and 100 mg./100ml. polyethylene glycol (PEG—Carbowax 4000). The pH of this solution was 6.8. All solutions were at ambient temperature when instilled. The first 225 ml. aliquot of test solution was then instilled, mixed gently by hand aspiration for 1 minute, and left in the stomach for 30 minutes. After its removal, three 10-minute washes were performed in a similar manner. The composition of test solution and wash solution was identical. The purpose of these instillations was to cleanse the stomach thoroughly and allow maximal adsorption of PEG to the gastric mucosa.[24] An additional quantitative wash with 225 ml. of test solution was then performed. Fifteen-minute flux periods were then immediately begun by instillation of 225 ml. of the same test solution which was mixed gently for 1 minute. After mixing, and "initial" 40 ml. sample was withdrawn, and a flux period commenced. Exactly 15 minutes later the residual gastric content was aspirated as the "final" sample for that flux period. Four identical, serial, 15-minute flux measurements were performed, each separated by a quantitative wash.

All samples were analyzed for the concentration of hydrogen (H^+), lithium (Li^+), sodium (Na^+), potassium (K^+), chloride (Cl^-), pepsin, and PEG. The concentration of H^+ was determined by electrometric titration to pH 7.0 with 0.1 N sodium hydroxide. The concentration of Li^+ was determined by atomic absorption spectrophotometry (model 205B Perkin-Elmer spectrophotometer). The concentrations of Na^+ and K^+ were determined by flame photometry with the use of a lithium standard. Chloride ion concentration was assessed by the Buchler–Cotlove chloridometer. The concentration of pepsin was determined by a modification of the method of Anson.[1] The concentration of PEG was assessed by the turbidimetric method of Malawer and Powell.[28]

Ion fluxes or changes in permeability were inferred by changes in the ratio of the concentration of ion to the concentration of PEG [Δ(ion/PEG)] from the initial to the final sample. The Δ(ion/PEG) ratios for the serial replicate 15-minute flux periods were averaged for each patient. An increase in the change of this ratio represents a positive ion flux (net gain of ion into the lumen), and a decrease in the Δ(ion/PEG) represents a negative ion flux (net loss of ion from the lumen). Thus, a greater than normal negative value for the mean $\Delta(Li^+/PEG)$ ratio reflects an abnormally large loss of lithium ion from the lumen, and, therefore, increased gastric mucosal permeability.[37] A change in intraluminal fluid volume produces an equal change in the concentration of ions and PEG and, therefore, does not affect the ratio. Similarly, pyloric loss of intraluminal content does not alter the ratio of ion to PEG.

Results

Flux Data

Mean flux data for the patients with neurosurgical illness are presented in Table 1. The 13 patients comprising the general surgical category were divided into two groups, one with normal and one with increased GMP. Previous studies of healthy volunteers[20,21] have shown that the normal mean $\Delta(Li^+/PEG)$ ratio is -0.13 ± 0.01. Flux data for the general surgical group with normal GMP ($\Delta(Li^+/PEG) \leqq -0.13$) are shown in Table 2, and those for the group of general surgical patients with increased GMP ($\Delta(Li^+/PEG) > -0.13$) are shown in Table 3. Previous studies of randomly selected similarly sick patients have shown that about one half will have increased GMP.[34]

The general surgical groups with increased GMP had a mean $\Delta(Li^+/PEG)$ ratio of -0.19 ± 0.01 (Fig. 1). Even though the separation of the general surgical patients into two groups was reasonably arbitrary, the value for those with increased GMP is significantly more negative ($p < 0.001$) than the mean $\Delta(Li^+/PEG)$ ratio of -0.11 ± 0.01 found in general surgical patients with normal GMP and is also significantly more negative ($p < 0.005$) than that of the neurosurgical group. The overall mean $\Delta(Li^+/PEG)$ ratio of -0.12 ± 0.02 for the neurosurgical patients is almost identical to that of general surgical patients with normal GMP and for normal individuals.[20,21]

The mean $\Delta(H^+/PEG)$ ratios, a reflection of gastric acid secretion, and Δ(pepsin/PEG) ratios of the three groups show a distinctly different trend (Figs. 1, 2). The ratios of $\Delta(H^+/PEG)$ and Δ(pepsin/PEG) are similar for both general surgical groups. However, the $\Delta(H^+/PEG)$ ratio of the neurosurgical patients is almost four times greater ($p < 0.03$) and the Δ(pepsin/PEG) is more than three times greater ($p < 0.03$) than those of the two general surgical groups. The mean $\Delta(Na^+/PEG)$ ratios reveal that the influx of sodium ion into the gastric lumen is greatest in the general surgical group with increased gastric mucosal permeability (Fig. 2).

Clinical Data

Striking clinical differences between the three groups are apparent (Tables 4–7 and Fig. 3). General surgical patients with increased permeability had the greatest number of complications (Table 7 and Fig. 3). This latter group had the highest mortality rate, and the greatest incidence of sepsis, hypotension, respiratory failure, jaundice and renal insufficiency. The neu-

TABLE 1. *Mean Flux Data for Neurosurgical Patients*

Patient	$\Delta(\mathrm{Li}^+/\mathrm{PEG})$	$\Delta(\mathrm{H}^+/\mathrm{PEG})$	$\Delta(\mathrm{Na}^+/\mathrm{PEG})$	$\Delta(\mathrm{K}^+/\mathrm{PEG})$	$\Delta(\mathrm{Cl}^-/\mathrm{PEG})$	Δ(Pepsin/PEG)
1. R. L.	−0.12	+9.3	+6.4	+2.8	+16.8	—
2. F. C. (I)	−0.04	+7.4	+1.1	+1.3	+9.8	—
3. F. C. (II)	−0.18	—	—	+0.7	—	—
4. J. C. (I)	−0.05	+5.5	+2.0	+0.5	+7.8	+131
5. J. C. (II)	−0.09	+1.8	+8.0	+1.4	+9.5	+122
6. J. W.	−0.11	+26.4	+5.1	+3.4	+35.0	—
7. F. C.	−0.10	+6.1	+2.1	+0.8	+7.1	+54
8. H. H.	−0.18	+0.8	+2.3	+0.3	+2.4	+110
9. K. F.	−0.16	+18.2	+3.4	+2.4	+24.0	+327
10. S. J.	−0.18	+24.7	−1.5	+2.4	+25.3	+295
11. I. L.	−0.06	—	−1.3	—	—	—
Mean	−0.12	+11.1	+2.8	+1.8	+15.3	+173.2
SEM	±0.02	±3.2	±0.9	±0.3	±3.6	±45.1
p (GS Norm GMP)	NS	<0.03	$.05 < p < 0.1$	<0.05	<0.03	<0.03
p (GS Incr GMP)	<0.005	<0.01	NS	<0.05	<0.05	<0.05

SEM: standard error of the mean; p(GS norm GMP): compared to general surgical group with normal permeability; p(GS: Incr GMP): compared to general surgical group with increased GMP. Patient F. C. (I) and (II) indicates 2 measurements at different times on patient F. C.

rosurgical patients and those general surgical patients with normal GMP had approximately the same incidence of these complications. Increasing severity of illness is paralleled by increasing GMP (Fig. 4). All patients with normal GMP had a mean incidence of 1.2 complications per patient compared to a mean incidence of 3.4 complications in those patients with increased GMP ($p < 0.01$). The relationship between severity of illness and increased GMP is particularly evident in neurosurgical patients. Nine of the 11 neurosurgical patients received intramuscular dexamethasone therapy, while none of the general surgical patients received this drug. Five of the neurosurgical patients receiving steroid medication had normal GMP. Steroid usage, therefore, as in experimental animal work,[2,8] cannot be implicated alone as a factor which results in abnormal GMP.

Gastric Bleeding

Gastric bleeding was defined as a gastric aspirate greater than 2+ guaiac for 3 consecutive hours in the 12-hour period prior to study. Using this criterion, ten of the 25 patients had gastric bleeding (Fig. 5). Bleeding was of minor clinical significance in all 10 patients, and none required more than one blood transfusion. Fifty per cent of the patients who bled were in the general surgical group with increased GMP and 50% were in the neurosurgical group. Gastric bleeding did not occur in any patient in the general surgical group with normal GMP. The occurrence of bleeding was correlated with the presence of an increased gastric mucosal permeability and to the presence of clinical features previously shown to be associated with acute gastrointestinal ulceration.[33,34] Patients who bled had a mean $\Delta(\mathrm{Li}^+/\mathrm{PEG})$ of −0.17 compared to a value of −0.12 for those who did not bleed ($p < 0.005$) and had 3.2 complications per patient (Table 7, Figs. 3–5) compared to an incidence of 1.7 complications per patient in nonbleeders ($0.05 < p < 0.1$). Neurosurgical patients who bled also had significantly increased GMP ($\Delta(\mathrm{Li}^+/\mathrm{PEG}) = -0.16$) in comparison to neurosurgical patients without gastric bleeding ($\Delta(\mathrm{Li}^+/\mathrm{PEG}) = -0.08$, $p < 0.001$). Neurosurgical patients who bled also had significantly more complications (2.6 per patient) than neurosurgical patients who did not bleed (0.8 complications per patient, $p < 0.05$). In addition, neurosurgical patients who bled had a mean $\Delta(\mathrm{H}^+/\mathrm{PEG}) = +12.5$ and a mean $\Delta(\mathrm{pepsin}/\mathrm{PEG}) = +197$ compared

TABLE 2. *Mean Flux Data for General Surgical Patients with Normal Gastric Mucosal Permeability*

Patient	$\Delta(\mathrm{Li}^+/\mathrm{PEG})$	$\Delta(\mathrm{H}^+/\mathrm{PEG})$	$\Delta(\mathrm{Na}^+/\mathrm{PEG})$	$\Delta(\mathrm{K}^+/\mathrm{PEG})$	$\Delta(\mathrm{Cl}^-/\mathrm{PEG})$	Δ(Pepsin/PEG)
1. S. M.	−0.13	+3.6	—	+1.6	—	—
2. J. T.	−0.13	+8.0	+2.1	+1.3	+10.8	+66
3. H. G.	−0.09	+0.8	−1.3	+0.4	+0.3	+8
4. A. M.	−0.07	+3.5	+5.4	+1.1	+9.0	+78
5. M. L.	−0.13	+0.3	−0.5	+0.2	−1.2	+32
6. E. S.	−0.12	+0.4	−2.5	+0.3	+0.8	—
Mean	−0.11	+2.8	+0.6	+0.8	+3.9	+46.0
SEM	±0.01	±1.2	±1.4	±0.2	±1.7	±15.9
p(NS)	NS	<0.03	$.05 < p < .1$	<0.05	<0.03	<0.03
p(GS Incr GMP)	<0.001	NS	NS	NS	NS	NS

p(NS): compared to neurosurgical group; p(GS incr GMP): compared to GS group with increased GMP.

TABLE 3. *Mean Flux Data for General Surgical Patients with Increased Gastric Mucosal Permeability*

Patient	$\Delta(\mathrm{Li}^+/\mathrm{PEG})$	$\Delta(\mathrm{H}^+/\mathrm{PEG})$	$\Delta(\mathrm{Na}^+/\mathrm{PEG})$	$\Delta(\mathrm{K}^+/\mathrm{PEG})$	$\Delta(\mathrm{Cl}^-/\mathrm{PEG})$	$\Delta(\mathrm{Pepsin}/\mathrm{PEG})$
1. I. W.	−0.20	+0.1	−0.1	−0.6	+0.2	+9
2. E. A.	−0.19	+2.7	+7.3	+1.3	+10.0	+136
3. L. B.	−0.20	+2.6	−0.7	+0.4	+1.1	+25
4. A. M. (I)	−0.22	+0.6	+18.4	+0.7	+23.8	+100
5. A. K.	−0.16	+0.1	−2.3	−0.3	−3.0	—
6. S. M.	−0.16	+4.4	+6.0	+0.4	+6.2	+28
7. T. Z.	−0.19	+5.4	+7.0	+0.8	+13.2	+78
8. M. M.	−0.20	+3.2	−2.5	+0.8	+2.6	+24
Mean	−0.19	+2.2	+4.1	+0.4	+6.5	+57.1
SEM	±0.01	±0.8	±2.5	±0.2	±3.1	±18.1
p(GS Norm)	<0.001	NS	NS	NS	NS	NS
p(NS)	<0.005	<0.01	NS	<0.05	<0.05	<0.05

p(GS norm): compared to general surgical group with normal permeability.
p(NS): compared to neurosurgical group.

to a mean $\Delta(\mathrm{H}^+/\mathrm{PEG}) = +10.1$ and a mean $\Delta(\mathrm{pepsin}/\mathrm{PEG}) = +127$ in neurosurgical patients who did not bleed (p = NS). However, the $\Delta(\mathrm{H}^+/\mathrm{PEG})$ and $\Delta(\mathrm{pepsin}/\mathrm{PEG})$ in neurosurgical patients who bled were significantly higher than general surgical patients who bled $\Delta(\mathrm{H}^+/\mathrm{PEG})$ in general surgical patients who bled $= +2.1$ ($p < 0.05$), and $\Delta(\mathrm{pepsin}/\mathrm{PEG}) = +72$, $0.05 < p < 0.1$). Therefore, neurosurgical patients who bleed are characterized by abnormally increased permeability in the presence of increased gastric acid secretion and increased pepsin secretion, a situation quite different from general surgical patients with bleeding in whom the GMP was increased while secretion of hydrogen ion and pepsin were not elevated. Sepsis, respiratory failure and significant periods of hypotension were individually or collectively present in the neurosurgical patients who bled in all instances.

Several patients with neurological injury or general surgical illness are of special interest:

Case Reports

Case 1. Patient F. C. (#38-66-47), a 55-year-old man, was studied 1 day following craniotomy for removal of a cerebellar tumor. The $\Delta(\mathrm{Li}^+/\mathrm{PEG})$ was −0.04. Increased intracranial pressure developed rapidly the next day, followed by respiratory arrest. Decompressive craniotomy for bleeding in the operative site was performed. He was restudied 2 days later. At this time he was comatose, in respiratory failure, and had intermittent periods of hypotension. The $\Delta(\mathrm{Li}^+/\mathrm{PEG})$ was now −0.18 and the gastric aspirate was 4+ guaiac.

Comment: The first study demonstrated that intracranial surgery without associated complications was associated with normal GMP. Following reoperation, at a time when hypotension and respiratory failure were present, a markedly increased GMP was observed.

Case 2. Patient K. F. (#45-62-56), a 22-year-old man, was admitted after a drug overdose complicated by aspiration pneumonia with fixed dilated pupils, a blood pressure of 70 mm. Hg, arterial pH = 7.14, P_{CO_2} = 52 mm. Hg, and base excess = −12. Following intermittent periods of hypotension with no resolution of his anoxic encephalopathy, the gastric aspirate was bloody (guaiac 4+). Study of GMP in this patient showed a $\Delta(\mathrm{Li}^+/\mathrm{PEG}) = -0.16$ and $\Delta(\mathrm{H}^+/\mathrm{PEG}) = +18.2$.

Comment: Complications of hypotension and aspiration pneumonia resulting in respiratory failure were associated with bleeding and increased GMP in this patient with anoxic encephalopathy.

Case 3. S. J. (#45-70-33), a 60-year-old woman, was admitted with severe frontal headache and bloody cerebrospinal fluid. Cerebral angiography showed an aneurysm of the right posterior communicating artery. Blood pressure was maintained at hypotensive levels (65 to 90 mm. Hg systolic) during operation and for the first 10 hours postoperatively. Gastric aspirate was 2+ to 3+ guaiac for 4 hours during the night preceding study. Study of GMP at this time showed a $\Delta(\mathrm{Li}^+/\mathrm{PEG}) = -0.18$ and $\Delta(\mathrm{H}^+/\mathrm{PEG}) = +24.7$.

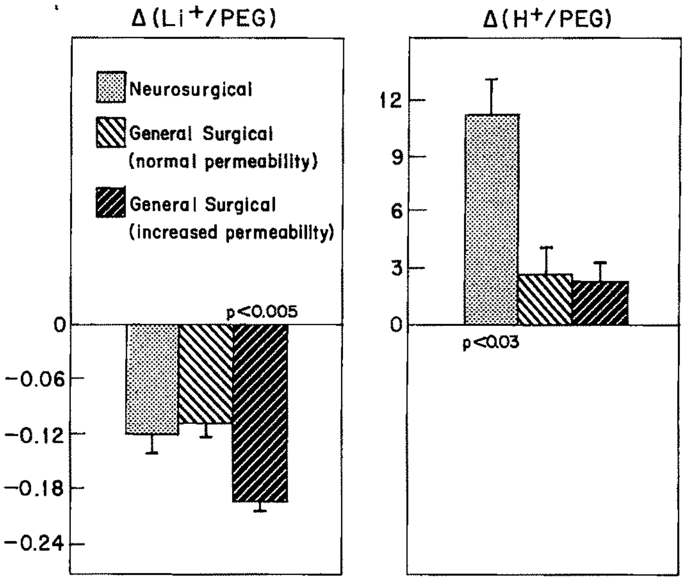


FIG. 1. *Lithium and Hydrogen Ion Flux Data.* Significantly increased gastric mucosal permeability [$\Delta(\mathrm{Li}^+/\mathrm{PEG})$] was present in general surgical patients with increased GMP in comparison to general surgical patients with normal GMP. Significantly increased gastric acid secretion [$\Delta(\mathrm{H}^+/\mathrm{PEG})$] was present in neurosurgical patients in comparison to both general surgical groups. (p values refer to general surgical group with normal GMP)

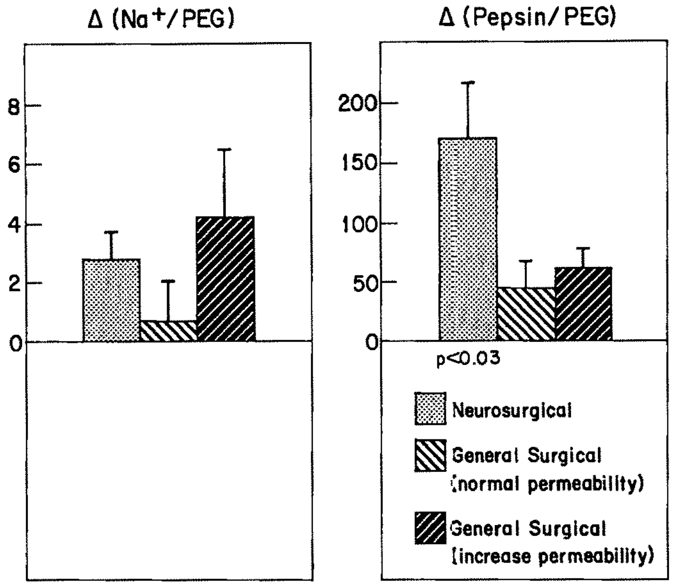


FIG. 2. *Sodium Ion and Pepsin Flux Data.* Influx of sodium into the lumen [$\Delta(Na^+/PEG)$] was greater in general surgical patients with increased GMP. Neurosurgical patients had a significantly greater pepsin secretion than patients in either general surgical group. (p value refers to patients in both general surgical groups)

Comment: Severe hypotension was associated with increased GMP and increased gastric acid secretion in this patient with a subarachnoid hemorrhage from a bleeding intracranial aneurysm.

Case 4. Patient J. C. (#45-13-98), a 51-year-old man, had a cerebral concussion with a scalp laceration, and underwent decompression and fusion of fractured C3-5 vertebrae with quadriplegia following an auto accident. When initially studied 1 week after admission he had a normal GMP ($\Delta(Li^+/PEG) = -0.05$). His subsequent clinical course was uneventful. Follow-up study 4 weeks later showed a $\Delta(Li^+/PEG) = -0.09$.

Comment: This study indicates the reproducibility of normal GMP measurements in a patient with neurological injury who did not develop any complications. (Cushing commented that Schiff, a pupil of Rokitansky, showed that hemisection of the upper two segments of the spinal cord in dogs would often lead to softening of the stomach and occasionally to actual perforation.)[10]

Case 5. Patient A. M. (#45-38-37), a 46-year-old lady, developed acute gastric dilatation 4 days after a jejuno-ileal bypass operation performed for obesity. She was studied 18 hours after decompression by nasogastric tube. At this time, the $\Delta(Li^+/PEG)$ was -0.22, the highest value observed in this series of patients. She was restudied 6 days later by which time normal gastrointestinal function had resumed. Her $\Delta(Li^-/PEG)$ fell to -0.07, a value well within the normal range.

Comment: Markedly increased GMP was observed in this patient with gastric bleeding after acute gastric dilatation. This study strongly suggests that the mucosal ischemia induced by gastric distension may cause an alteration in gastric mucosal permeability with subsequent hemorrhage, a physiological aberration which is reversible with time.

Discussion

Gastric mucosal permeability (GMP) and gastric acid secretion were assessed in 13 patients with general surgical illness and nine patients with neurosurgical illness. Gastric mucosal permeability was determined by measurement of the change in the lithium ion to polyethylene glycol ratio.[6,7,20,21,37] The general surgical patients were arbitrarily divided into approximately two equal sized groups based on the finding of normal or increased GMP. The mean flux data reveal that as a group, patients with neurosurgical disease have normal gastric mucosal permeability and markedly increased acid and pepsin secretion in comparison to general surgical patients. An increased concentration of acid and pepsin[23] and increased gastric acid secretion[29] have previously been demonstrated in patients with intracranial injury. Hypersecretion of acid and pepsin in such patients may be secondary to stimulation of the anterior nuclei of the hypothalamus. Experimental work in cats has indicated increases in left gastric artery blood flow and acid secretion occur in response to such stimulation.[26] Regardless of the state of GMP, patients in the general surgical groups have very low secretion of acid and pepsin.

The $\Delta(H^+/PEG)$ ratio reflects acid secretion modified by back diffusion. It is possible that an increased back diffusion of H^+ resulting from an increase in GMP in these seriously ill general surgical patients could mask an occult increase in acid secretion. However, the absence of a substantial increase in pepsin secretion in these patients suggests, but does not prove,

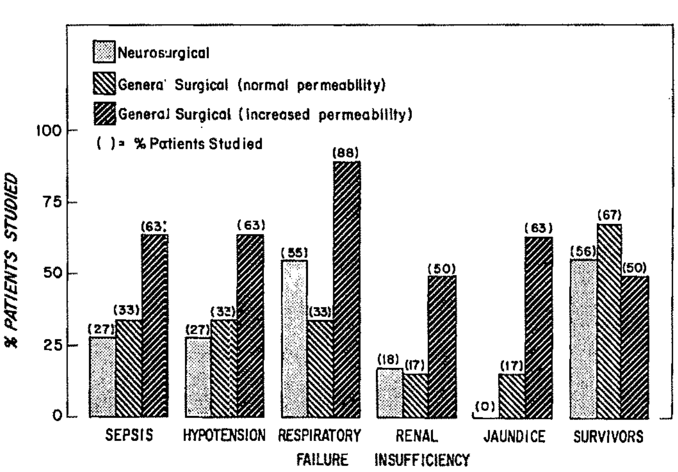


FIG. 3. *Pertinent Clinical Features of Patient Groups.* General surgical patients with increased GMP had the greatest incidence of complications and the lowest survival rate. General surgical patients with normal GMP and neurosurgical patients had approximately the same incidence of complications.

TABLE 4. *Clinical Data—Neurosurgical Patients*

Patient Hosp #	Diagnosis	Age Sex	Hct	Creat.	Bilirubin	Steroids (Decadron)	Sepsis	Hypo- tension	Resp. Failure	Gastric Bleeding	Survivor
1. R. L. 44–42–02	Cerebral hematoma & contusion 2 d. post-auto accident	70M	34	1.2	0.8	4 mg. q6° 4 d	No	No	48°	No	No
2. F. C. (I) 38–66–47	Cerebellar carcinoma 1 d. post-resection	55M	38	0.8	0.8	4 mg. q6° 3 d	No	No	No	No	Yes
3. F. C. (II) 38–66–47	Decompressive craniotomy, resp. arrest—2 d. postop., 4 d. post-resection	55M	36	1.2	1.0	4 mg. q6° 7 d	No	Yes	72°	Yes	Yes
4. J. C. (I) 45–13–98	Fracture C3-5 with quadriplegia 1 w. post-decompression & fusion	51M	36	0.9	0.7	None	No	No	No	No	Yes
5. J. C. (II) 45–13–98	Fracture C3-5 with quadriplegia 5 w. postop.	51M	38	0.8	0.8	None	No	No	No	No	Yes
6. J. W. 42–00–21	Berry aneurysm MCA 5 d. post-coating	33F	42	1.1	0.8	4 mg. q6° 10 d	No	No	No	No	Yes
7. F. C. 45–56–94	Bilat. subdural hematoma 2 d. post-evac.	74M	34	1.2	1.0	4 mg. q6° 2 d	Lung *E. coli*	No	48°	Yes	Yes
8. H. H. 45–64–02	Skull fx—cerebral contusion 3 d. post-trauma	35M	42	1.3	1.0	4 mg. q6° 3 d.	Lung Klebsiella	No	72°	Yes	No
9. K. F. 45–62–56	Narc. overdose—anoxic brain damage—3 d. post-adm.	23M	46	3.9	0.9	4 mg. q6° 4 d.	Lung *E. coli*	Yes	96°	Yes	No
10. S. J. 45–70–33	Berry aneurysm PCA 1 d. post-clipping	60F	43	0.9	0.6	4 mg. q6° 2 d.	No	Yes	No	Yes	Yes
11. I. L. 45–80–61	Cerebellar tumor 2 d. post-resection	61M	32	1.9	0.7	4 mg. 6q° 4 d.	No	No	48°	No	No
MEAN ± SEM		51.5 ±6.2	37 ±2.2	1.5 ±0.3	0.8 ±0.1						

Sepsis: Significant clinical infection requiring specific treatment; Hypotension: Blood pressure less than 80 mm. Hg for more than 15 minutes at least in the 12 hours prior to study; Gastric Bleeding: Gastric aspirate more than 2+ guaiac for more than 3 consecutive hours in the 12 hours prior to study; MCA: middle cerebral artery; PCA: posterior cerebral artery; Hct: hematocrit (%); Creat.: serum creatinine (mg./100 ml.).

that true hyposecretion of acid was present. This argument is strengthened by the observation that those general surgical patients with increased GMP did not secrete nearly as much pepsin as the neurosurgical patients with increased or normal GMP despite the fact that Johnson[25] has shown that disruption of the mucosal barrier is associated with a marked release of pepsin into gastric juice.

Davenport[11–14] has shown that a disrupted gastric mucosal barrier is associated with an increased mucosa to lumen flux of sodium ions. The present data indicate that the greatest increase of $\Delta(Na^+/PEG)$ occurred in patients in the general surgical group with significantly increased mucosal permeability even though statistically significant differences were not reached.

The clinical data reveal that the group of general surgical patients with increased GMP had a substantially higher incidence of sepsis, hypotension, respiratory failure, renal insufficiency, and jaundice than either the neurosurgical group or the general surgical group with normal GMP. This finding is in agreement with previous studies of critically ill patients.[34] The positive correlation between severity of illness and gastric mucosal permeability is also observed within the neurosurgical group, where patients with increased permeability generally had the greatest number of associated complications. Patient F. C. is illustrative of this relationship. After an uncomplicated craniotomy he had an elevated acid output compared to the general surgical patients and a normal GMP. During a series of complications which included hypotension and respiratory failure, restudy showed markedly increased GMP and 4+ guaiac gastric aspirate. In contrast, patient J. C., who had a cerebral concussion and quadriplegia secondary to C3-5 fracture, maintained a normal GMP during a 4-week postoperative course which was not associated with any complications.

Gastric bleeding, defined by a gastric aspirate more than 2+ guaiac for more than 3 consecutive hours in the 12 hours prior to study, occurred in 10 of 25 studies performed in the 22 patients. Bleeding was associated with increased gastric mucosal permeability in nine of the ten studies. A relationship between increased gastric mucosal permeability and bleeding from the stomach has been previously suggested.[34,36] This concept is strongly supported by these data. The incidence of gastric mucosal bleeding in all patients was correlated with the number of associated complications. No instances of bleeding were found in the group of general surgical patients with normal GMP. Patients of this latter group also had the lowest incidence of complications.

Four of the five neurosurgical patients with gastric bleeding had significantly increased GMP, and the

TABLE 5. *Clinical Data—General Surgical Patients with Normal Gastric Mucosal Permeability*

Patient Hosp #	Diagnosis	Age Sex	Hct	Creat.	Bilirubin	Sepsis	Hypo-tension	Resp. Failure	Gastric Bleeding	Survivor
1. S. M. 40–59–34	Severe viral pneumonia, tension pneumothorax, tracheostomy	19M	36	0.8	0.6	Bilat. viral pneumonia	Yes	96°	No	No
2. J. T. 34–03–87	Carcinoma cecum 1 d. post-right colectomy	86M	33	1.2	0.7	No	No	No	No	Yes
3. H. G. 45–35–42	Carcinoma rectum 1 d. post-A-P resection	69M	38	1.2	0.8	No	No	No	No	Yes
4. A. M. (II) 45–38–37	4 d. post-acute gastric dilatation	46F	39	0.9	0.7	No	No	No	No	Yes
5. M. L. 45–58–92	Celiac artery graft—ATN-hepatic failure—8 d. postop.	27F	34	4.2	6.8	Lung Klebsiella	Yes	7d	No	No
6. E. S. 33–08–53	Carcinoma pancreas 2 d. post-laparotomy	60M	31	0.7	0.5	No	No	No	No	Yes
MEAN ± SEM		51.2 ±8.3	35 ±0.8	1.5 ±0.8	1.7 ±0.7					

ATN: acute tubular necrosis of kidneys.

number of associated complications were significantly increased in the neurosurgical patients who bled compared to patients in this group who did not bleed. Hypotension was prominent among these complications and formed a significant part of their clinical course. The occurrence of an increased GMP and increased number of associated complications was similar in the neurosurgical patients that bled. However, neurosurgical patients who bled also showed a significantly higher $\Delta(H^+/PEG)$ and $\Delta(\text{pepsin}/PEG)$ than general surgical patients who bled. Thus, acid and pepsin output remained high despite an increase in gastric mucosal permeability. This important difference suggests that neurosurgical patients with a similar degree of hypotension, sepsis, respiratory failure and other complications may be even more prone to develop acute stress ulceration because of gastric acid hypersecretion and increased pepsin secretion. The character and extent of bleeding seen in the present group of patients with neurological disease would appear to be distinctly different from the clinical course and pathology of patients with classical Cushing's ulcers.[10] Cushing described a group of nine patients who had massive bleeding from deeply penetrating ulcers of the duodenum and stomach, but in six patients he found curious areas of complete gastric and esophageal wall dissolution which Cushing called "esophagomalacia" or "gastromalacia." Cushing also described two patients with "antemortem mucosal erosions" and specifically commented that the vomitus of patients who had intracranial surgery often contained traces of blood. These two patients are probably similar to the patients of the present neurosurgical group and are distinctly more typical of acute stress ulcers seen in most sick patients. Thus, neurosurgical patients with increased GMP probably have an ischemic injury super-

TABLE 6. *Clinical Data—General Surgical Patients with Increased Gastric Mucosal Permeability*

Patient Hosp #	Diagnosis	Age Sex	Hct	Creat.	Bilirubin	Sepsis	Hypo-tension	Resp. Failure	Gastric Bleeding	Survival
1. I. W. 41–17–13	Cholangitis & sepsis—2 d. CBDE & sphincterotomy	72M	36	1.2	2.8	Cholangitis *E. coli*	Yes	24°	No	Yes
2. E. A. 45–35–44	Aortic aneurysm—ATN 4 d. post-graft	61F	32	2.5	6.1	No	Yes	48°	Yes	Yes
3. L. B. 45–46–24	Gallstone ileus, asp. pneumonia, renal failure-6 d. postop.	79F	38	6.2	4.3	Lung: *E. coli* Klebsiella	Yes	4d	Yes	No
4. A. M. (I) 45–38–37	1 d. post-acute gastric dilatation, 5 d. post-jejuno-ileal bypass	46F	34	0.8	1.2	No	No	No	Yes	Yes
5. A. K. 31–71–14	Perf. appendix, peritonitis 2 d. postop.	78F	35	1.4	0.9	Peritonitis *E. coli*	No	24°	Yes	No
6. S. M. 40–23–22	Cholangitis, septic shock renal failure—2 d. postop.	87F	34	4.0	5.2	Cholangitis *E. coli* Klebsiella	Yes	24°	Yes	No
7. T. Z. 45–64–42	Gastritis, UGI bleed, pneumonia, 7 d. post-adm.	73F	35	2.6	1.9	Lung *S. aureus*	No	7d	No	No
8. M. M. 45–90–52	Aortic aneurysm 2 d. post-graft	75F	34	0.8	0.6	No	Yes	24°	No	Yes
MEAN ± SEM		71.5 ±4.2	34 ±0.9	2.4 ±0.8	2.9 ±0.4					

CBDE: common bile duct exploration.

TABLE 7. *Summary of Clinical Data of the Three Patient Groups*

	Sepsis	Hypotension	Resp. Insuff.	Renal Failure	Janudice	Survivors	Gastric Bleeding	Group Totals
Neurosurg.	3/11 27%	3/11 27%	6/11 55%	2/11 18%	0/11 —	5/9 56%	5/11 45%	24/11
Gen'l Surg. Normal GMP	2/6 33%	2/6 33%	2/6 33%	1/6 17%	1/6 17%	4/6 67%	0/6 —	12/6
Gen'l Surg. Increased GMP	5/8 63%	5/8 63%	7/8 88%	4/8 50%	5/8 63%	4/8 50%	5/8 63%	35/8
Totals	10/25	10/25	15/25	7/25	6/25	13/22	10/25	71/25

Sepsis: Significant clinical infection requiring specific treatment; Hypotension: Systemic blood pressure less than 80 mm. Hg for more than 15 minutes at least in the 12 hours prior to study.

imposed on the basic abnormal pathophysiology associated with the intracranial lesion.

Most of the neurosurgical patients were receiving steroids. Although steroids themselves do not alter gastric mucosal permeability,[8] they do enhance the effect of other agents that do.[2] The routine use of steroids to prevent cerebral swelling in neurosurgical patients who have been shown to have a higher acid output, especially when multiple complications are present, may be a particularly ulcerogenic combination and strongly suggests the need for aggressive antacid prophylaxis in these patients.

It has been demonstrated in the rabbit that increased gastric transmural pressure markedly increases gastric mucosal permeability.[4] This experimental model was duplicated clinically in patient A.M. who had acute gastric dilatation with bleeding at a time when GMP was markedly elevated. When normal peristalsis resumed, a repeat study demonstrated GMP had returned to a normal value.

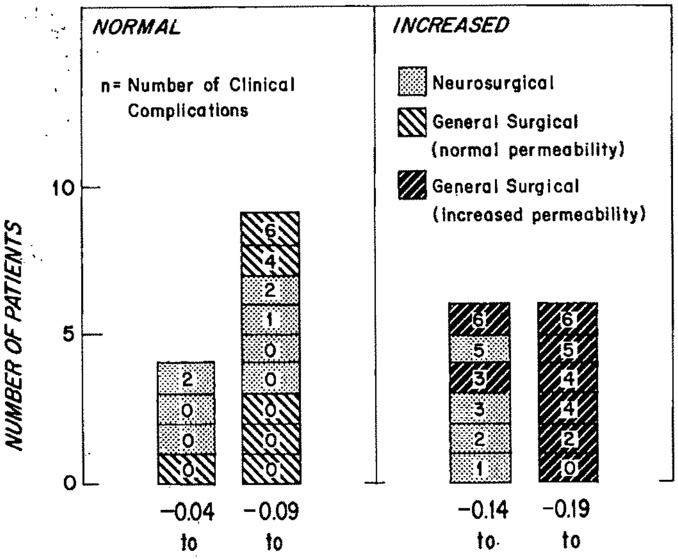


FIG. 4. *Degree of Gastric Mucosal Permeability Related to Patient Group and Associated Clinical Features.* Increasing severity of illness is paralleled by increasing gastric mucosal permeability [$\Delta(Li^+/PEG)$]. (Normal = patients with normal GMP; Increased = patients with increased GMP; each box represents one patient and the number in the box indicates the number of clinical complications.

Summary

An acid-free NaCl-LiCl technic was used to assess alterations in gastric mucosal permeability (GMP) and gastric acid secretion in 13 patients with general surgical illness and nine patients with neurosurgical illness. Gastric mucosal permeability and gastric acid secretion were estimated by the change in the ratio of $\Delta(Li^+/PEG)$ and $\Delta(H^+/PEG)$ respectively.

Six of the 13 acutely ill general surgical patients had normal GMP. The remaining seven general surgical patients had increased GMP. Hypotension, sepsis, re-

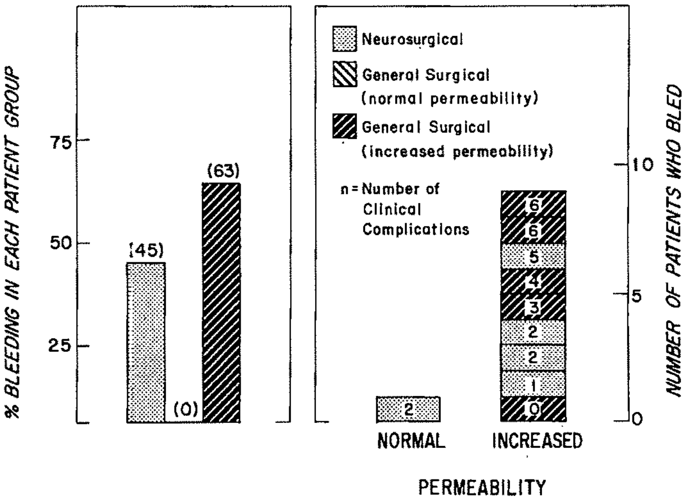


FIG. 5. Per cent bleeding in each patient group (left hand); permeability and number of associated clinical complications in each patient who bled (right hand). No general surgical patients with normal GMP bled (left hand). Only one patient with normal GMP bled (right hand). Five of the nine patients with increased GMP who bled had more than two associated complications (Each box in the right hand figure represents one patient and the number in the box indicates the number of clinical complications).

spiratory failure, renal insufficiency, jaundice and death occurred more frequently in the group with increased GMP.

The group of nine neurosurgical patients had normal GMP, but greatly increased gastric acid secretion in comparison to the sickest group of general surgical patients who show increased GMP and low acid secretion.

Gastric bleeding not requiring more than 1 unit of blood transfusion occurred prior to study in ten of the 22 patients. Four of the five patients with neurological injury who bled, and all of the five general surgical patients who bled had increased GMP, but the former group also have a significantly increased gastric acid secretion and pepsin secretion. Patients who bled also had a significantly increased number of clinical complications compared to the patients who did not bleed. A relationship between increased GMP and bleeding from the stomach is strongly supported by these investigations. Patients with neurological injury complicated by hypotension and respiratory failure may develop the same kind of ulceration seen in general surgical patients who bleed. It is likely that classical Cushing's ulcerations of the deeply penetrating or perforating variety is a distinctly different clinical entity.

References

1. Anson, M. L.: The Estimation of Pepsin, Trypsin, Papain, and Cathepepsin with Hemoglobin. J. Gen. Physiol., **22**: 79, 1932.
2. Aubrey, D. A. and Burns, G. P.: Topically Administered Prednisolone and the Antral Phase of Gastric Secretion. Arch. Surg., **105**:448, 1972.
3. Beil, A. R., Jr., Mannix, H., Jr. and Beal, J. M.: Massive Upper Gastrointestinal Hemorrhage after Operation. Am. J. Surg., **108**:324, 1964.
4. Bulkley, G., Goldman, H. and Silen, W.: Pressure Injury to the Gastric Mucosa—Studies on an *in vivo* Model of Acute Gastric Dilatation. Am. J. Surg., **117**:193, 1969.
5. Chapman, M. A., Werther, J. L. and Janowitz, H. D.: Response of the Normal and Pathological Human Gastric Mucosa to an Instilled Acid Load. Gastroenterology, **55**: 344, 1968.
6. Chung, R. S. K., Field, M. and Silen, W.: Gastric Mucosal Permeability to Hydrogen and Lithium: A New Method for Quantitation of the Gastric Mucosal Barrier. Surg. Forum, **21**:297, 1970.
7. Chung, R. S. K., Field, M. and Silen, W.: Permeability of Gastric Mucosa to Hydrogen and Lithium. Gastroenterology, **64**:593, 1973.
8. Chung, R. S. K., Field, M. and Silen, W.: Gastric Permeability to H^+: Effects of Prednisolone and Acetylsalicylic Acid on the Coefficient of H^+ Diffusion. Gastroenterology, **58**:1038, 1970.
9. Curling, T. B.: On Acute Ulceration of the Duodenum in Cases of Burn. Med. Chir. Trans., **25**:260, 1842.
10. Cushing, H.: Peptic Ulcers and the Interbrain. Surg., Gynecol. Obstet., **55**:1, 1932.
11. Davenport, H. W.: Gastric Mucosal Injury by Fatty and Acetylsalicylic Acids. Gastroenterology, **46**:245, 1964.
12. Davenport, H. W.: Damage to the Gastric Mucosa: Effects of Salicylates and Stimulation. Gastroenterology, **49**:189, 1965.
13. Davenport, H. W.: Destruction of the Gastric Mucosal Barrier by Detergents and Urea. Gastroenterology, **54**:175, 1968.
14. Davenport, H. W.: Is the Apparent Hyposecretion of Acid by Patients with Gastric Ulcer a Consequence of a Broken Barrier to Diffusion of Hydrogen Ions into the Gastric Mucosa? Gut, **6**:513, 1965.
15. Davenport, H. W.: Physiology of the Digestive Tract. Chicago, Year Book Publishers, 1971, p. 98.
16. Fischer, R. P. and Stremple, J. F.: Stress Ulcers in Post-traumatic Renal Insufficiency in Patients from Viet Nam. Surg., Gynecol. Obstet., **134**:790, 1972.
17. Fletcher, D. G. and Harkins, H. N.: Acute Peptic Ulcer as a Complication of Major Surgery, Stress or Trauma. Surgery, **36**:212, 1954.
18. Fogelman, J. J. and Garvey, J. M.: Acute Gastrointestinal Ulceration Incident to Surgery and Disease: Analysis and Review of 88 Cases. Am. J. Surg., **112**:651, 1966.
19. Goodman, A. A. and Frey, C. F.: Massive Upper Gastrointestinal Hemorrhage following Surgical Operations. Ann. Surg., **167**:180, 1968.
20. Gordon, M. J., Skillman, J. J. and Silen, W.: Assessment of Human Gastric Mucosal Permeability by an Acid-free Technique. Gastroenterology, **62**:846, 1972.
21. Gordon, M. J., Skillman, J. J. and Silen, W.: An Acid-free Technique to Study Human Gastric Mucosal Permeability: Effect of Ethanol and Acetylsalicylic Acid. Surg. Forum, **23**:384, 1972.
22. Grosz, C. R. and Wu, K. T.: Stress Ulcers: A Survey of the Experience of a Large General Hospital. Surgery, **61**:853, 1967.
23. Idjadi, F., Robbins, R., Stahl, W. M. and Essiet, G.: Prospective Study of Gastric Secretion in Stressed Patients with Intracranial Injury. J. Trauma, **11**:681, 1971.
24. Ivey, K. J. and Schedl, H. P.: Gastric Nonabsorbable Indicators for Studies in Man. Gastroenterology, **59**:534, 1970.
25. Johnson, L. R.: Pepsin Secretion during Damage of the Gastric Mucosa by Ethanol and Acetylsalicylic Acid. Gastroenterology, **62**:412, 1972.
26. Leonard, A. S., Long, D., French, L. A. and Wangensteen, O. H.: Pendular Pattern of Gastric Secretion and Blood Flow Following Hypothalmic Stimulation. Surgery, **56**: 109, 1964.
27. Leurate, M., Lambert, R. and Malluret, J.: Acute Gastroduodenal Ulcers and Digestive Hemorrhage Provoked by Surgical Interventions. Acta. Chir. Belg., **65**:549, 1966.
28. Malawer, S. J. and Powell, D. W.: An Improved Turbidimetric Analysis of Polyethylene Glycol Utilizing an Emulsifier. Gastroenterology, **53**:250, 1967.
29. Norton, L., Greer, J. and Eiseman, B.: Gastric Secretory Response to Head Injury. Arch. Surg., **101**:200, 1970.
30. Overholt, B. F. and Pollard, H. M.: Acid Diffusion into the Human Gastric Mucosa. Gastroenterology, **54**:182, 1968.
31. Overholt, B. F. and Pollard, H. M.: Acetylsalicylic Acid and Ion Fluxes across the Gastric Mucosa of Man. Gastroenterology, **54**:538, 1968.
32. Sevitt, S.: Duodenal and Gastric Ulceration after Burning. Brit. J. Surg., **54**:32, 1967.
33. Skillman, J. J., Bushnell, L. S., Goldman, H. and Silen, W.: Respiratory Failure, Hypotension, Sepsis and Jaundice—A Clinical Syndrome Associated with Lethal Hemorrhage from Acute Stress Ulceration of the Stomach. Am. J. Surg., **117**:523, 1969.
34. Skillman, J. J., Gould, S. A., Chung, R. S. K. and Silen, W.:

The Gastric Mucosal Barrier: Clinical and Experimental Studies in Critically Ill and Normal Man, and in the Rabbit. Ann. Surg., 172:564, 1970.

35. Skillman, J. J. and Silen, W.: Acute Gastroduodenal "Stress" Ulceration: Barrier Disruption of Varied Pathogenesis? Gastroenterology, 59:478, 1970.

36. Skillman, J. J. and Silen, W.: Stress Ulcers. Lancet, 2:87, 1972.

37. Smith, B. M., Skillman, J. J., Edwards, B. G. and Silen, W.: Permeability of the Human Gastric Mucosa: Alteration by Acetylsalicylic Acid and Ethanol. N. Engl. J. Med., 285:716, 1971.

38. Wlodek, G.: Discussion of: Skillman, J. J. *et al.* The Gastric mucosal Barrier: Clinical and Experimental Studies in Critically Ill and Normal Man, an in the Rabbit. Ann. Surg., 172:583, 1972.

DISCUSSION

DR. FRANK G. MOODY (Salt Lake City): Dr. Gordon and his colleagues have clearly demonstrated with ultra-sophisticated technics in the neurosurgical patient and possibly the patient with head injury has increased acid output.

The major thrust of their study, however, is to demonstrate in the very sick patient that indeed there is a change in the barrier to ions, especially hydrogen back diffusion through the mucosa. This raises, at least in my mind, two important questions in the data.

The first relates to the observation that in the very sick patient there is an increased loss of lithium from the stomach, presumably into or through the epithelium. This is associated with an increased output of sodium, but there is no change in the rate of hydrogen production in the sick general surgical patient versus the very sick patient. If indeed there was a change in the barrier, then one could barely detect hydrogen secretion in the lumen of the stomach in this situation.

The second problem relates to the observation that there is no increase in lithium loss in the surgical patient who does not have hypotension or sepsis. Could it be that in this patient with increased hydrogen secretion, there is restriction to movement of lithium down into the tubules thereby giving less of a surface area for lithium diffusion, thereby masking the possibility there may indeed be increased lithium loss in these patients.

My own bias is going away from the back diffusion concept as an etiology of stress ulcer, at least as a requisite etiology for it has been observed that in the dog with hypotension and acid placed on the surface of the stomach, there is no increase in back diffusion. Recently we have learned that with direct infusion of endotoxin, one can produce gastric erosions with actually a decrease in acid back diffusion.

I would appreciate the authors' comments in terms of their present concept of the etiological significance of the mucosal barrier.

DR. C. THOMAS FITTS (Charleston): I would like to congratulate the authors on this evidence in humans that one of the particular categories of acute ulceration, namely Cushing's ulcer is probably patho-physiologically distinct from at least one other category, that of acute ulceration from non-specific stress.

It fits well with evidence from experimental animals in the laboratory and with the clinical work of Watts and Clark in Dallas and Norton and Eiseman in Denver, among others.

This is, I believe, the type of information which as it gradually accumulates will allow us to treat acute ulcerations more logically and therefore probably with better results in the future.

I have one question. I would like to know if the authors have any study in progress that would measure this parameter in any of the other categories of stress ulcer, such as steroid or in the burn patient with the Curling's ulcer.

DR. JOHN J. SKILLMAN (Closing): Dr. Moody has raised some interesting questions which I do not believe can be answered from the work that we presented. All we can say along these lines is that when an injury occurs to the gastric mucosal surface of the stomach, the stomach becomes more permeable to the lithium ion. Other *in vitro* experiments which have recently been performed in Dr. Silen's laboratory by Dr. Desmond Birkett indicate that when there is injury to the gastric mucosa, there is a change in permeability to other ions and other substances. For example, non-metabolized sugars such as mannitol and erythritol will also pass through a damaged gastric mucosa in increased amounts. It is also clear from the experimental data in animals that ischemia causes an increase in gastric mucosal permeability.

Dr. Fitts raised the important question about the effect of steroids. It is interesting that in the neurosurgical group of patients that we have reported here, a number of these patients, I think five out of the total group, had no increase in permeability even though they were receiving steroids, so that steroids by themselves do not cause an increase in permeability. Experimental work in animals has indicated that steroids do enhance the effect of other agents which damage the gastric mucosa and, therefore, cause a greater back diffusion of ions than is produced by the damaging agent alone.

In summary, I would like to say that the work we presented today supports and extends some previous observations that we reported before this group several years ago. What we are showing here is that the neurosurgical group is really a different group from sick general surgical patients in that the neurosurgical patients have an increase in acid output and increase in pepsin secretion. However, when patients in the neurosurgical group develop multiple complications, there is an increase in the permeability of their gastric mucosa that makes them very similar to the general surgical patients with multiple complications. Multiple complications in any group of patients seem to be associated with an increased risk of bleeding and we should worry about these patients when trying to ascertain which patients might develop acute gastric ulceration.

Effect of Proximal Gastric, Complete Gastric, and Truncal Vagotomy on Canine Gastric Electric Activity, Motility, and Emptying

BRUCE G. WILBUR, M.D., KEITH A. KELLY, M.D.

From the Section of Surgical Research, Mayo Clinic and the Mayo Medical School, Rochester, Minnesota 55901

PROXIMAL GASTRIC VAGOTOMY without a "drainage" procedure is currently under trial as an operative treatment for duodenal ulcer.[2,11,13,20] The proponents state that the operation effectively decreases the secretion of HCl and pepsin by the stomach, thereby allowing the ulcer to heal, while preserving normal gastric motility.[1,2,11-13,20] Indeed, fewer postoperative side effects have been reported after proximal gastric vagotomy than after several other anti-ulcer operations.[2,4,8,11-13,18-20,24,29,33] However, the effect of proximal gastric vagotomy on gastric motility and emptying has not been extensively studied.

Our hypothesis is that the vagally innervated proximal stomach regulates gastric emptying of liquids by controlling gastric transmural pressure and that the vagally innervated antrum regulates gastric emptying of solids by controlling the terminal antral contraction. Thus, proximal gastric vagotomy should speed gastric emptying of liquids but not alter gastric emptying of solids, while complete gastric vagotomy or truncal vagotomy should speed emptying of liquids and slow emptying of solids. We tested this hypothesis in dogs by studying gastric transmural pressure and gastric emptying of liquids and solids before and after proximal gastric, complete gastric, and truncal vagotomy.

Materials and Methods

Five healthy, mongrel, female dogs, 8 to 12 Kg. in weight, were used. They were alert and conscious during all observations and had been fasted at least 18 hours. The dogs also were conditioned to the passage of an oral-gastric tube.

Four sets of control experiments were done in the dogs before vagotomy. In the first set of experiments, performed four times in each dog, gastric transmural pressure was measured before and during gastric distention with a flaccid, plastic bag of capacity greater than 800 ml. Gastric transmural pressure is that pressure due solely to contractions of the gastric wall. The pressure was recorded as the difference between the pressure inside and that outside the gastric wall.

The pressure inside the stomach was measured by connecting a pressure transducer (Statham P23Dd) via an oral-gastric tube to the plastic bag used to distend the stomach. The pressure outside the gastric wall was measured using a sterile, plastic catheter (ID 1 mm) placed intraperitoneally and attached via a three-way connector to a second transducer. A continuous infusion of 154 mM NaCl at 0.1 ml./min was given through the third channel of the connector to keep the intraperitoneal catheter patent. The infusion did not alter the pressure recorded from this catheter. The electric signals from the two pressure transducers were fed into a differential amplifier, and the difference between the two signals was recorded (Heathkit Servo recorder). The apparatus was calibrated before and after each experiment by the use of water manometers.

The intragastric bag was inserted through the dog's mouth into the stomach, anchored in place using a bite block, and then distended with water at 37.5°C,

---

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25-27, 1973.

This investigation was supported in part by Research Grant AM-2015 from the National Institutes of Health, Public Health Service.

first to 50 ml., and then to 100 ml., and finally, in 100-ml. increments, to 800 ml. Continuous records of the gastric transmural pressure were obtained for 3 minutes at each volume of distention, and the mean pressure was later calculated from the area under each 3-minute curve.

In the second set of prevagotomy experiments, gastric emptying of 400 ml. of 154 mM NaCl with 0.00035% polyethylene-1, 2-^{14}C-glycol (PEG, New England Nuclear) of specific activity 0.6 mCi/g was assessed five times in each dog. An oral-gastric tube was inserted, and the saline was instilled into the stomach during a period of 30 to 45 seconds. The tube was then removed. The instillate was at 37.5°C when given, and had a pH of approximately 6.5. Ten minutes after instillation, the gastric tube was reinserted and the gastric content was withdrawn by siphoning and gentle aspiration with a syringe. The stomach was washed with 100 ml of saline, and the wash was aspirated to recover any residual instillate. If particulate matter was found on aspiration of the original instillate, the experiment was discarded.

At the completion of each test, the volumes of gastric aspirate and gastric wash recovered were measured. The specific activities of 5-ml. samples of original instillate, aspirate, and wash were determined using the liquid scintillation spectrometer (Packard Tri-Carb 3375). The volume of instillate emptied from the stomach in the 10-minute period was then calculated using the following formulas:

$$(1) \qquad V_L = 400 - V_R \quad \text{and}$$

$$(2) \qquad V_R = V_A \cdot \frac{SA_A}{SA_I} + V_W \cdot \frac{SA_W}{SA_I},$$

in which V_L represents the volume of the original instillate emptied from the stomach in 10 minutes, 400 ml. is the volume originally instilled, V_R is the volume of the original instillate remaining in the stomach at 10 minutes, V_A is the volume of the gastric aspirate, V_W is the volume of the gastric wash, and SA_I, SA_A, SA_W are the specific activities of the instillate, gastric aspirate, and gastric wash, respectively.

A third set of control experiments, performed five times in each dog, was done in an identical fashion to the above, except that a 400-ml. instillate of 500 mM glucose with 0.00035% PEG was used instead of the saline instillate.

In the last set of control experiments, gastric emptying of 40 solid plastic spheres was assessed five times in each dog. The spheres were made of polypropylene (Orange Products, N.J.) and were 7.14 mm. in diameter. They were made radiopaque by imbedding two small lead pellets in their center; this also increased their specific gravity to approximately 1.02. The spheres were placed in the dog's stomach via an oral-gastric tube, and the tube was removed. The number of spheres emptied from the dog's stomach was determined fluoroscopically every 30 minutes with the dogs in their normal prone (lying) position until all spheres had emptied or 8 hours had passed. The pattern of gastric motor activity was also noted. A similar technic has been used in this laboratory in the past.[31]

The dogs were operated on while under anesthesia with pentobarbital given intravenously, and a proximal gastric vagotomy was performed (Fig. 1). All structures between the anterior nerve of Latarjet and the lesser curvature of the stomach from the esophagogastric junction to the point of passage of the nerve onto the gastric antrum were then ligated and divided as close to the stomach as possible (Fig. 1 *A*).[20] Through an opening in the greater omentum, a similar procedure was done on the posterior side of the stomach, preserving the pos-

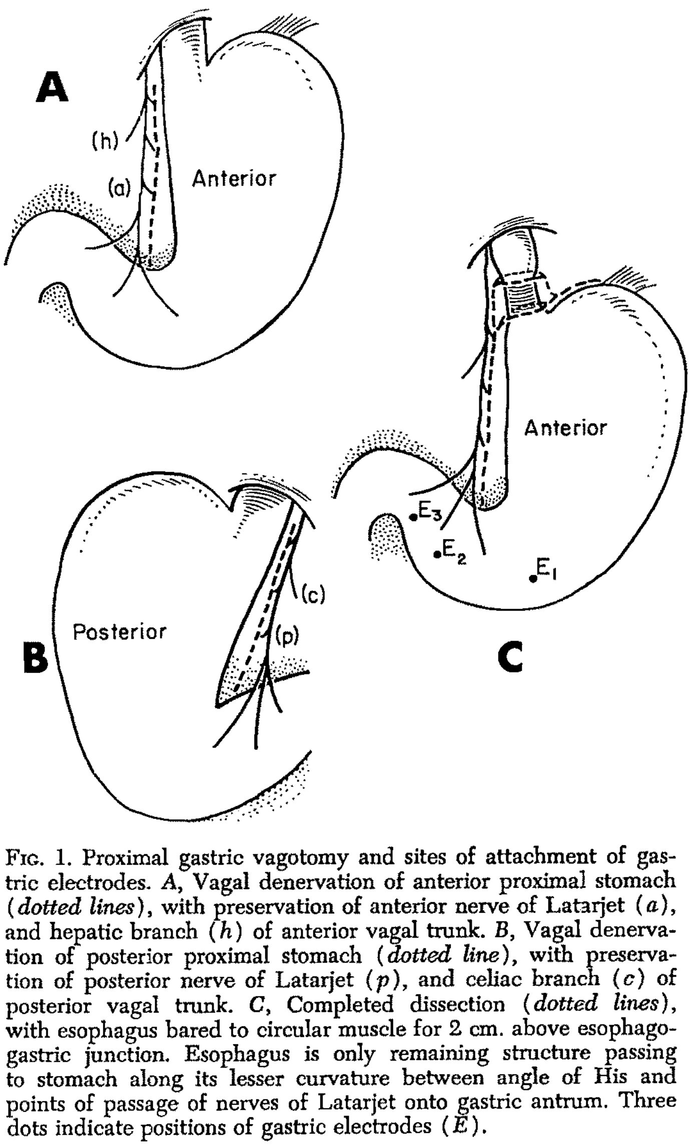


FIG. 1. Proximal gastric vagotomy and sites of attachment of gastric electrodes. *A*, Vagal denervation of anterior proximal stomach (*dotted lines*), with preservation of anterior nerve of Latarjet (*a*), and hepatic branch (*h*) of anterior vagal trunk. *B*, Vagal denervation of posterior proximal stomach (*dotted line*), with preservation of posterior nerve of Latarjet (*p*), and celiac branch (*c*) of posterior vagal trunk. *C*, Completed dissection (*dotted lines*), with esophagus bared to circular muscle for 2 cm. above esophagogastric junction. Esophagus is only remaining structure passing to stomach along its lesser curvature between angle of His and points of passage of nerves of Latarjet onto gastric antrum. Three dots indicate positions of gastric electrodes (*E*).

terior nerve of Latarjet (Fig. 1 *B*). The distal esophagus was then mobilized, and all tissue external to the circular muscle layer was divided for a distance of 2 cm. above the esophagogastric junction. This step ensured division of any additional vagal fibers coursing along the esophagus from the proximal vagal trunks to the stomach. At this point, the bared esophagus was the only structure passing to the stomach along the lesser curvature between the angle of His and the points of passage of the anterior and posterior nerves of Latarjet onto the gastric antrum (Fig. 1 *C*).

Monopolar silver wire electrodes were then implanted on the gastric wall. The electrodes were used primarily to enable us to verify whether vagal innervation of the antrum was intact or disrupted after recovery from the operations. When vagal innervation of the antrum is intact, action potentials appear in the antral electric tracings within 15 to 25 minutes after insulin is given intravenously.[22]

Each electrode was 1 mm in diameter and projected 1½ to 2 mm. from a dental acrylic (Acrolite) disk. The shafts of the electrodes were insulated with vinyl paint, but the tips were exposed and AgCl was deposited electrolytically on them. Each electrode was soldered to a Teflon-insulated copper lead 12 inches long, and the soldered junction was encased within and insulated by the acrylic disk. Epoxy resin was used to seal the points at which electrode and wire penetrated the disk surface. Two holes and one notch were made in the disk to facilitate fixation to the gastric wall. The insulated lead from each disk was connected to a pin of a radiotube socket mounted with epoxy resin and dental acrylic in a stainless steel cannula.

Three electrodes were sutured to the anterior serosal surface of the stomach 2 cm. from the greater curvature at positions 8, 4, and 2 cm. from the pylorus. The metal cannula to which the copper leads were attached was positioned in and sutured to the left anterior abdominal wall in the midclavicular line.

The dogs were allowed 1 month to recover from the operation, after which experiments identical to those done before vagotomy were repeated during the second postoperative month. In addition, on separate days, gastric electric activity was recorded in each dog for 10 minutes before and 45 minutes after the intravenous injection of 1.5 units/Kg. of regular insulin.

The dogs were then operated upon a second time, and the gastric antrum was vagally denervated (Fig. 2 *A*). All structures passing to the stomach along the lesser curvature from the esophagogastric junction to 1 cm. beyond the gastroduodenal junction, including the nerves of Latarjet, were ligated and divided as close to the gastric wall as possible. The duodenum was then circumscribed down to, but not through, the longitudinal muscle at a level 1 cm. aborad to the gastroduodenal junction. The greater omentum was also ligated and divided along a line about 1 cm. from the greater curvature from the duodenum to the approximate junction of gastric antrum and corpus. This operation, coupled with the first operation (proximal gastric vagotomy), effected a complete gastric vagotomy.

The dogs were allowed 1 month to recover from the complete gastric vagotomy, after which experiments identical to those performed after proximal gastric vagotomy were repeated.

The dogs were then operated upon a third time, and a transthoracic truncal vagotomy was performed at a level about 5 cm. above the diaphragm (Fig. 2 *B*). After a 1-month recovery, identical tests to those done before vagotomy were repeated.

The dogs were then sacrificed, and autopsies were performed.

Results

The dogs tolerated all three operations and the electric apparatus well. They remained healthy throughout the experiment.

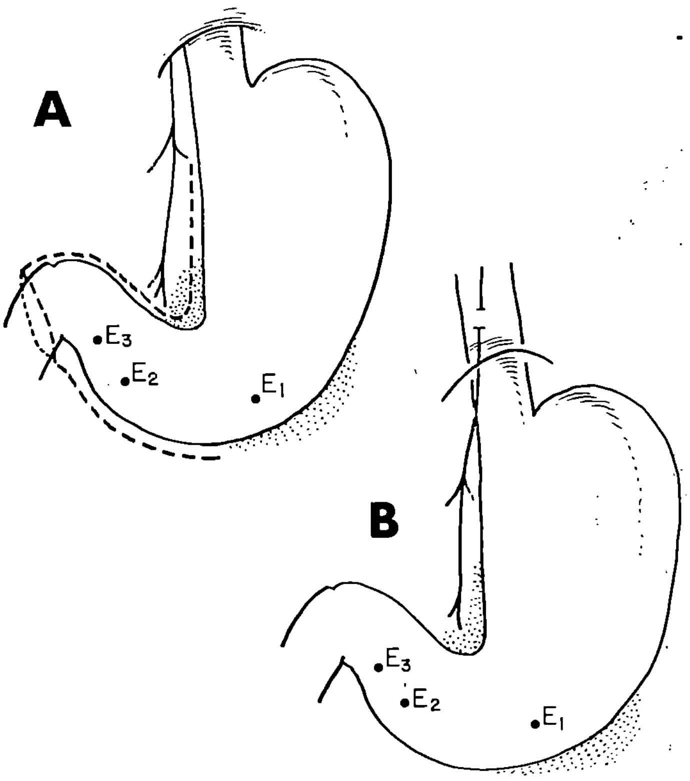


FIG. 2. *A*, Vagal denervation of gastric antrum. *Dotted lines* along greater and lesser curvatures indicate transection and those around duodenum 1 cm. beyond gastroduodenal junction indicate incision down to but not through longitudinal muscle. Anterior and posterior nerves of Latarjet are schematically represented by one nerve. This procedure, together with proximal gastric vagotomy (Fig. 1), effected a complete gastric vagotomy. *B*, Truncal vagotomy. One-centimeter segments of vagal trunks were excised about 5 cm. above diaphragm, and both cut ends tied.

Before Vagotomy. Gastric Transmural Pressure. Gastric transmural pressure was successfully measured in four of the five dogs. Dog E would not tolerate the oral-gastric tube and intragastric bag long enough for satisfactory measurements to be made.

Gastric transmural pressure increased slowly and gradually with gastric distention. The mean pressure increased from 5.0 to 14.0 cm. H_2O as the intragastric bag was distended from 50 to 800 ml. (Fig. 3). The overall mean slope of the regression of pressure on volume was 1.2 cm. H_2O/100 ml.

Gastric Emptying. Gastric emptying of *liquids* was also successfully measured in only four of the five dogs. Again, dog E would not tolerate the instillations.

The dogs emptied a mean of 121 ml. of the saline instillate and a mean of 26 ml. of the glucose instillate from the stomach in 10 minutes. The rate of emptying of glucose was significantly slower than that of saline (Table 1, $p < 0.01$).

The overall pattern of the gastric movement of *spheres* in dogs before vagotomy was one of retention of spheres in the antrum, with continuous vigorous mixing and grinding interspersed between periodic bursts of emptying.

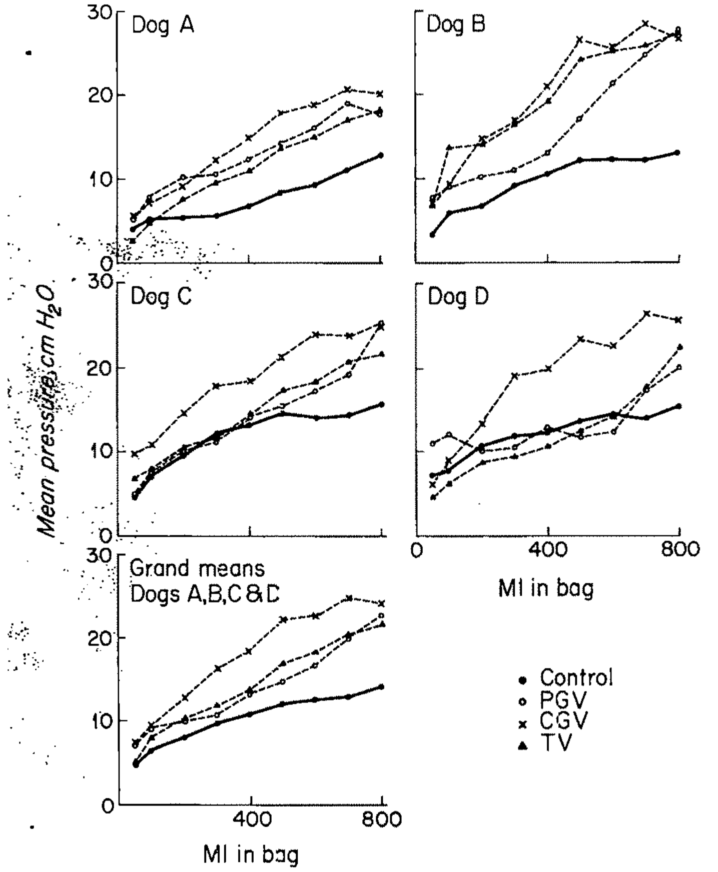


FIG. 3. Gastric transmural pressure increased more with distention of intragastric bag after proximal gastric (PGV), complete gastric (CGV), and truncal vagotomy (TV) than it did before vagotomy. For each dog, each point represents mean of four experiments. For grand means, each point represents mean of 16 experiments.

TABLE 1. *Effect of Proximal Gastric (PGV), Complete Gastric (CGV), and Truncal Vagotomy (TV) on Gastric Emptying of Liquids*

	Mean ml. emptied in 10 minutes*							
	NaCl, 154 mM				Glucose, 500 mM			
		After				After		
Dog	Before vagotomy	PGV	CGV	TV	Before vagotomy	PGV	CGV	TV
A	115	200	207	159	9	102	139	83
B	80	199	266	230	21	79	211	131
C	151	195	224	174	14	87	159	125
D	139	207	155	92	61	138	92	58
Grand mean	121	200	213	164	26	102	150	99

* Each value for individual dog is mean of five experiments. Grand means are means of 20 experiments. SE was less than 30 for all values except NaCl of dog C after PGV, when it was 37. For significance, see text.

The spheres passed through the oral-gastric tube directly into the fundus and proximal corpus of the stomach. They were then promptly moved into the distal corpus and antrum where they were continuously mixed and ground by peristalsis and the terminal antral contraction. An advancing peristaltic wave propelled the spheres up against the gastroduodenal junction. The spheres were then squeezed by the forceful terminal antral contraction, until, unable to pass into the duodenum, they suddenly shot back into the more proximal antrum and distal corpus. This propulsion, squeezing, and retropulsion occurred over and over, thoroughly triturating the spheres.

At certain times, as a peristaltic wave approached the terminal antrum, bunches of spheres would be moved rapidly from the terminal antrum through the gastroduodenal junction into the duodenum. Sometimes, all 40 spheres would be emptied within a 30-minute period. However, the overall mean time from insertion to completion of gastric emptying was 2.2 hours (Fig. 4).

After Proximal Gastric Vagotomy. Electric Activity. Electric recordings were satisfactory in four of the five dogs. The electrodes in dog D "shorted out" in the early postoperative period.

A cyclic variation in potential, the gastric pacesetter potential,[23] was consistently detected in the gastric wall 1 month after proximal gastric vagotomy. The cycles were always present and generally appeared in a regular rhythm at a frequency of about five cycles per minute (Fig. 5). The frequency was usually identical at all recording sites. However, the duration of the cycles sometimess varied from one cycle to another (Fig. 5 *upper left* and *lower right*), an occurrence that is uncommon in dogs with normal stomachs.[23] Also, in two of the four dogs, episodes of completely disorganized gastric electric activity were found occasionally during fasting (Fig. 6), a phenomenon also rare in normal dogs, but more common in dogs after truncal vagotomy.[22]

Action potentials, the electric activity associated with contractions,[23] occurred intermittently with the cycles of the pacesetter potential before the injection of insulin (Fig. 5). But, insulin stimulated the appearance of action potentials with every cycle of the antral pacesetter potential within 20 minutes of its administration in every test in every dog (Fig. 5). Thus, vagal innervation of the antral musculature was intact.[22]

Gastric Transmural Pressure. After proximal gastric vagotomy, gastric transmural pressure increased more rapidly with distention than it did before vagotomy. The pressure increased from a mean of 7 cm. H_2O to a mean of 23 cm. H_2O as the intragastric bag was distended from 50 to 800 ml. (Fig. 3). The overall mean slope of the regression of pressure on volume was 1.9 cm. H_2O/100 ml. This slope was greater than that found before vagotomy ($p < 0.01$). In all dogs but dog D, individual mean slopes were also greater after proximal gastric vagotomy than before ($p < 0.01$). However, even in dog D, when the intragastric bag contained 700 and 800 ml., the pressure was greater after proximal gastric vagotomy than it was before vagotomy.

Gastric Emptying. Proximal gastric vagotomy speeded gastric emptying of liquids (both saline and glucose instillates) compared to before vagotomy (Table 1, $p < 0.01$). But, glucose still emptied more slowly than saline in all four dogs after proximal gastric vagotomy ($p < 0.01$).

In contrast to the speeding of emptying of liquids after proximal gastric vagotomy, there was no significant change in the rate of emptying of *spheres* compared to before vagotomy. Also, the pattern of movement of spheres noted fluoroscopically was unaltered. The overall mean emptying time of 1.5 hours did not differ significantly from the 2.2 hours found before vagotomy.

After Complete Gastric Vagotomy. Electric Activity. After complete gastric vagotomy, the pattern of fasting, gastric, electric activity was similar to that found after proximal gastric vagotomy. However, insulin no longer triggered the onset of action potentials in any of the four dogs tested after complete gastric vagotomy (Fig. 5). Thus, vagal innervation of the antrum was no longer intact.[22]

Gastric Transmural Pressure. After complete gastric vagotomy, gastric transmural pressure increased from a mean of 7 cm. H_2O to a mean of 24 cm. H_2O as the intragastric bag was distended from 50 to 800 ml. (Fig. 3). The overall mean slope of the regression of pressure on volume was 2.4 cm. H_2O/100 ml. This slope was greater than that obtained before vagotomy ($p < 0.01$) but was not different from that found after proximal gastric vagotomy. In all four dogs, the individual mean slopes were greater than before vagotomy ($p < 0.01$). In dog D alone, there was an increase in slope between proximal gastric vagotomy and complete gastric vagotomy.

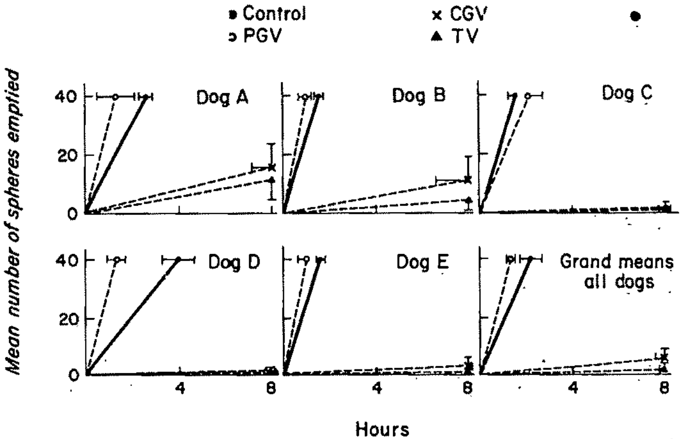


FIG. 4. Mean hours required to empty 40 radiopaque solid spheres from stomach were not significantly altered after proximal gastric vagotomy (PGV), but were greatly lengthened by complete gastric (CGV) and truncal vagotomy (TV). For individual dogs, each point is mean of five experiments. For grand means, each point is mean of 25 experiments. Standard error indicated by bars.

Gastric Emptying. After complete gastric vagotomy, *liquids* (both saline and glucose) continued to empty faster than before vagotomy ($p < 0.05$ and 0.01, respectively), but neither instillate emptied faster than it did after proximal gastric vagotomy. Glucose still emptied slower than saline after complete gastric vagotomy ($p < 0.01$).

In contrast to proximal gastric vagotomy, complete gastric vagotomy markedly slowed the rate of emptying of *spheres* compared to before vagotomy (Fig. 4). After the spheres were inserted into the stomach, they were promptly moved into the distal corpus and antrum, just as they were before vagotomy and after proximal gastric vagotomy. But the peristaltic waves, though present, were weak and often faded out in the antrum after complete gastric vagotomy, never reaching the pylorus. In addition, the terminal antral contraction was also weak and ineffective with little propulsion or retropulsion of spheres taking place.

The overall mean time from insertion to complete emptying of spheres was greater than 8 hours in the dogs after complete gastric vagotomy, compared to 2.2 and 1.5 hours noted before vagotomy and after proximal gastric vagotomy, respectively (Fig. 4, $p < 0.01$). In only 2 of 25 experiments did the dogs empty all spheres in 8 hours or less after complete gastric vagotomy. On some occasions, the spheres remained in the stomach for as long as 3 days.

After Truncal Vagotomy. Gastric Transmural Pressure. Gastric transmural pressure increased from a mean of 5 cm. H_2O to a mean of 22 cm. H_2O as the stomach was distended from 50 ml. to 800 ml. (Fig. 3). The overall mean slope of the regression of pressure on volume was 2.1 cm. H_2O/100 ml. and was greater than that found before vagotomy ($p < 0.01$) but was not different from that after proximal gastric vagotomy or complete gastric vagotomy. In all four dogs, individual mean slopes were greater than before vagotomy (p 0.01). In no dog was there a change in slope between complete gastric vagotomy and thoracic truncal vagotomy.

Gastric Emptying. After truncal vagotomy, *liquids* (both saline and glucose) emptied more slowly than they did after complete gastric vagotomy (Table 1, $p < 0.01$), so that the rate of emptying of saline no longer differed from that before vagotomy, although glucose still emptied faster than it did before vagotomy ($p < 0.01$). Glucose continued to empty more slowly than saline after truncal vagotomy ($p < 0.01$).

The rate of emptying of *spheres* was just as slow after truncal vagotomy as it was after complete gastric vagotomy. The sluggish motor activity noted fluoroscopically after complete gastric vagotomy was also found after truncal vagotomy. In all experiments, the dogs required 8 hours or more to empty the spheres from their stomachs (Fig. 4). The spheres often remained in the stomach for several days.

Postmortem Findings. At autopsy, minimal deposition of fibrous tissue was present around the electrodes, but no adhesions were found between the stomach and other abdominal organs. There was no evidence of mechanical obstruction of the stomach, the gastroduodenal junction, or the small or large bowel. A metal probe, diameter 1.5 cm., could be passed across the gastroduodenal junction without difficulty. The gastric and duodenal mucosa appeared normal, with no evidence of ulceration or inflammation. Postresection scarring prevented identification of structures along the lesser curvature, but the vagal trunks along the thoracic esophagus could be found, and all had been ligated and severed. One dog (dog D) had an extremely distended gallbladder, but no obstruction could be found in the cystic or common ducts, and no gallstones were present.

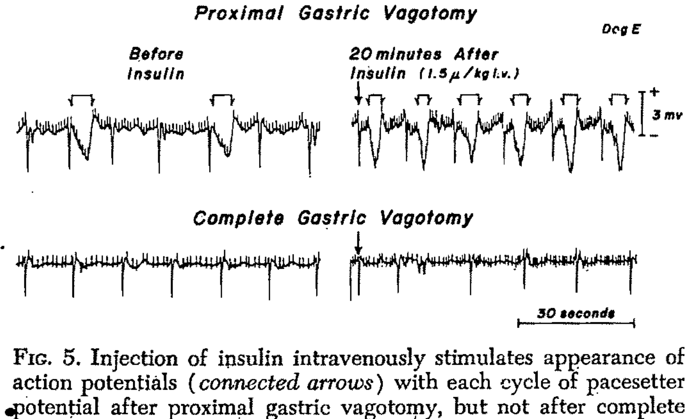


FIG. 5. Injection of insulin intravenously stimulates appearance of action potentials (*connected arrows*) with each cycle of pacesetter potential after proximal gastric vagotomy, but not after complete gastric vagotomy. All recordings from electrode E_3.

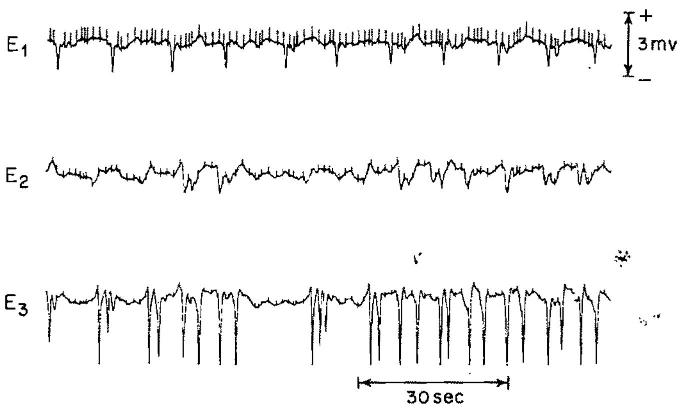


FIG. 6. Episode of disorganized gastric electric activity occurring 1 month after proximal gastric vagotomy in dog E. Frequency of gastric pacesetter potential is different at all three recording sites and increases to 18 cycles/min for brief periods at E_3. *E*, electrode.

Discussion

Our experiment shows that proximal gastric vagotomy preserves gastric motility and emptying better than complete gastric or truncal vagotomy. However, proximal gastric vagotomy does not leave gastric motility unaltered.

The fundus and proximal corpus of the stomach act as a reservoir, relaxing to receive and store ingested food.[5] As a result of this accommodation by the proximal stomach, gastric transmural pressure increases very little with increasing gastric distention.[36]

The vagal nerves have an important role in the accommodation of the stomach to distention. Others have found that greater increases in intragastric pressure occurred with gastric distention when the vagal nerves were transected,[27,30,32] and that electric stimulation of the distal cut ends of the vagal trunks could relax a distended stomach.[28] Our experiment supports these findings. Furthermore, our data show that it is the proximal gastric vagal fibers that mediate this response.

Humphrey and Wilkinson[13] have reported that early satiety and a sensation of epigastric fullness occur in patients after proximal gastric vagotomy. These symptoms are consistent with the failure of relaxation and accommodation to ingesta by the fundus and corpus.

We found that gastric emptying of isotonic saline and hypertonic glucose was consistently speeded after proximal gastric vagotomy. Clarke and Williams[6] also found that hypertonic glucose emptied faster after proximal gastric vagotomy than before vagotomy, but Humphrey and Wilkinson[13] did not. The explanation for the discrepancy between our findings and those of Humphrey and Wilkinson is unclear. Perhaps because Humphrey and Wilkinson did not compare gastric emptying in the same subjects before and after proximal gastric vagotomy, they were unable to detect a change.

Gastric emptying of liquids occurs when the intraluminal pressure in the stomach exceeds that in the duodenum and the pylorus is open.[35] Greater pressures in the stomach have been correlated with faster gastric emptying.[36] Thus, the increased gastric pressure caused by the failure of the stomach to accommodate to distention after proximal gastric vagotomy found in these experiments is responsible for the speeding of gastric emptying of liquids that we noted after the operation.

The impaired ability of the stomach to secrete HCl after proximal gastric vagotomy may have contributed to the increased speed of gastric emptying that we found after the operation. Hunt and Knox[14] have shown that acids slow gastric emptying. Thus, if less acid was secreted in response to the instillates after proximal gastric vagotomy, gastric emptying would be faster. However, the amount of acid secreted in response to the instillates used in these experiments was most likely very small. Furthermore, any speeding of gastric emptying brought about by a decreased secretion of HCl would be antagonized by the concurrent augmented release of gastrin also accompanying a more alkaline gastric pH.[10,17] Gastrin slows gastric emptying of liquids.[15] Further experiments are needed, but it seems unlikely that decreased secretion of acid by the stomach after proximal gastric vagotomy explains the marked speeding in gastric emptying of liquids that we found.

The rapid gastric emptying of liquids brought about by proximal gastric vagotomy persisted after complete gastric vagotomy. However, after truncal vagotomy, emptying of both saline and glucose solutions was slower than it was after complete gastric vagotomy. Transection of the extragastric abdominal vagi may result in the increased release of an extragastric hormone that slows gastric emptying, such as gastrin,[25,26] secretin, or cholecystokinin. But, the exact mechanism of the slowing when the extragastric vagi are cut is unknown.

We found that hyperosmolar glucose emptied more slowly than isotonic saline after each of the three vagotomies. Thus, the mechanism by which the duodenal osmoreceptors slow gastric emptying is not solely dependent on vagal pathways.

In contrast to the proximal stomach, which stores ingesta and regulates the gastric emptying of liquids, the distal stomach regulates the gastric emptying of solids. The terminal antral contraction rhythmically and forcefully propels and retropels solids, mixing and grinding them, and breaking them apart.[5] Solids are retained in the stomach by the terminal antral contraction until they are reduced to a size small enough for discharge into the duodenum. The antrum, thus, regulates the gastric emptying of solids.[7]

The pace of gastric peristalsis and of terminal antral contractions is set by a gastric pacemaker located in the orad corpus along the greater curve.[34] The pacemaker regularly generates gastric pacesetter potentials which sweep aborad in the gastric wall and phase the onset of peristaltic and terminal antral contractions.[23] Vagal denervation of the pacemaker by proximal gastric vagotomy disturbed its regularity slightly during fasting and occassionally allowed multiple, ectopic, rapid pacemakers to appear in the distal stomach. These disturbances, however, were not great enough to alter gastric motor responses to solid spheres.

Proximal gastric vagotomy, by preserving antral vagal innervation, preserved the terminal antral contraction, so that the pattern of gastric emptying of spheres was unchanged after the operation. Others have also observed that antral contractions are not greatly altered by proximal gastric vagotomy,[3,9,21] and that gastric emptying of food mixed with contrast media is normal.[12,13,16] In contrast, when the antrum was denervated by complete gastric or truncal vagotomy in our experiments, the terminal antral contraction was greatly impaired, resulting in a marked slowing of gastric emptying of spheres.

Summary

Proximal gastric vagotomy disturbed canine gastric motility and emptying less than did complete gastric vagotomy or truncal vagotomy. Although all three vagotomies increased gastric transmural pressure with gastric distention and speeded gastric emptying of liquids, only proximal gastric vagotomy preserved the terminal antral contraction and did not slow gastric emptying of solids. Our experiments identify the key role of the vagally innervated proximal stomach in regulating gastric emptying of liquids by controlling gastric transmural pressure and the key role of the vagally innervated antrum in regulating gastric emptying of solids by controlling the terminal antral contraction.

Acknowledgment

The authors thank Dr. Richard C. La Force for his helpful advice.

References

1. Amdrup, B. M. and Griffith, C. A.: Selective Vagotomy of the Parietal Cell Mass. Part I. With Preservation of the Innervated Antrum and Pylorus. Ann. Surg., 170:207, 1969.
2. Amdrup, E. and Jensen, H. E.: Selective Vagotomy of the Parietal Cell Mass Preserving Innervation of the Undrained

Antrum: A Preliminary Report of Results in Patients With Duodenal Ulcer. Gastroenterology, 59:522, 1970.

3. Bass, P., Walker, G. D. and Stewart, J. J.: The Effect of Parietal Cell and Truncal Vagotomy on Antral and Duodenal Contractile Activity of the Unanesthetized Dog (abstract). Gastroenterology, 62:838, 1972.
4. Burge, H., MacLean, C., Stedeford, R., Pinn, G. and Hollanders, D.: Selective Vagotomy Without Drainage: An Interim Report. Br. Med. J., 3:690, 1969.
5. Cannon, W. B.: The Mechanical Factors of Digestion. New York, Longmans, Green & Co., Inc., 1911.
6. Clarke, R. J. and Williams, J. A.: Prevention of "Dumping" by Retaining Antral Innervation. Surg. Forum, 23:329, 1972.
7. Dozois, R. R., Kelly, K. A. and Code, C. F.: Effect of Distal Antrectomy on Gastric Emptying of Liquids and Solids. Gastroenterology, 61:675, 1971.
8. George, J. D., Connell, A. M. and Kennedy, T.: Gastric Emptying in Patients With Post-Vagotomy Diarrhoea (abstract). Gut, 9:732, 1968.
9. Griffith, C. A. and Harkins, H. N.: Partial Gastric Vagotomy: An Experimental Study. Gastroenterology, 32:96, 1957.
10. Hansky, J., Korman, M. G., Coupland, G. A. E. and Cumberland, V. H.: Studies of Gastrin Release After Truncal, Selective and Highly Selective Vagotomy (abstract). Aust. NZ J. Med., 2:325, 1972.
11. Hedenstedt, S. and Moberg, S.: Selective Proximal Vagotomy With and Without Pyloroplasty in the Treatment of Duodenal Ulcer. Acta Chir. Scand., 137:547, 1971.
12. Humphrey, C. S., Johnston, D., Walker, B. E., Pulvertaft, C. N. and Goligher, J. C.: Incidence of Dumping After Truncal and Selective Vagotomy With Pyloroplasty and Highly Selective Vagotomy Without Drainage Procedure. Br. Med. J., 3:785, 1972.
13. Humphrey, C. S. and Wilkinson, A. R.: The Value of Preserving the Pylorus in the Surgery of Duodenal Ulcer. Br. J. Surg., 59:779, 1972.
14. Hunt, J. N. and Knox, M. T.: The Slowing of Gastric Emptying by Four Strong Acids and Three Weak Acids. J. Physiol. (Lond), 222:187, 1972.
15. Hunt, J. N. and Ramsbottom, N.: Effect of Gastrin II on Gastric Emptying and Secretion During a Test Meal. Br. Med. J., 4:386, 1967.
16. Interone, C. V., Del Finado, J. E., Miller, B., Bombeck, C. T. and Nyhus, L. M.: Parietal Cell Vagotomy: Studies of Gastric Emptying and Observations of Protection From Histamine-Induced Ulcer. Arch. Surg., 102:43, 1971.
17. Jaffe, B. M., Clendinnen, B. G., Clarke, R. J. and Williams, J. A.: Gastrin Response to Selective and Parietal Cell Vagotomies. Surg. Forum, 23:324, 1972.
18. Johnston, D., Humphrey, C. S., Smith, R. B. and Wilkinson, A. R.: Should the Gastric Antrum Be Vagally Denervated if It Is Well Drained and in the Acid Stream? Br. J. Surg., 58:725, 1971.
19. Johnston, D., Humphrey, C. S., Walker, B. E., Pulvertaft, C. N. and Goligher, J. C.: Vagotomy Without Diarrhoea. Br. Med. J., 3:788, 1972.
20. Johnston, D. and Wilkinson, A. R.: Highly Selective Vagotomy Without a Drainage Procedure in the Treatment of Duodenal Ulcer. Br. J. Surg., 57:289, 1970.
21. Kelly, J. M. and Kennedy, T. L.: Does Highly Selective Vagotomy Preserve Antral Motility (abstract)? Gut, 12:866, 1971.
22. Kelly, K. A. and Code, C. F.: Effect of Transthoracic Vagotomy on Canine Gastric Electrical Activity. Gastroenterology, 57:51, 1969.
23. Kelly, K. A., Code, C. F. and Elveback, L. R.: Patterns of Canine Gastric Electrical Activity. Am. J. Physiol., 217:461, 1969.
24. Klempa, I., Holle, F., Brückner, W., Welsch, K. H., Handle, H. and von Wolff, A.: The Effect of Selective Proximal Vagotomy and Pyloroplasty on Gastric Secretion and Motility in the Dog. Arch. Surg., 103:713, 1971.
25. Korman, M. G., Hansky, J., Coupland, G. A. E. and Cumberland, V. H.: Serum Gastrin in Duodenal Ulcer. Part IV. Effect of Selective Gastric Vagotomy. Gut, 13:163, 1972.
26. Korman, M. G., Soveny, C. and Hansky, J.: Extragastric Gastrin. Gut, 13:346, 1972.
27. Köster, N. and Madsen, P.: The Intragastric Pressure Before and Immediately After Truncal Vagotomy. Scand. J. Gastroenterol., 5:381, 1970.
28. Martinson, J. and Muren, A.: Excitatory and Inhibitory Effects of Vagus Stimulation on Gastric Motility in the Cat. Acta Physiol. Scand., 57:309, 1963.
29. Parkin, G. and Johnston, D.: Gall-Bladder Size and Emptying After Truncal, Selective, and Highly Selective Vagotomy in Man (abstract). Br. J. Surg., 59:306, 1972.
30. Rowe, C. R., Jr., Grimson, K. S., Flowe, B. H., Lyons, C. K., Longino, F. H. and Taylor, H. M.: Early and Late Effects of Vagotomy on Gastric Secretions and Motility. Surgery, 32:226, 1952.
31. Schlegel, J. F., Coburn, W. M., Jr. and Code, C. F.: Gastric Emptying of Solid and Compliant Spheres in Dogs (abstract). Physiologist, 9:283, 1966.
32. Stadaas, J. and Aune, S.: Intragastric Pressure/Volume Relationship Before and After Vagotomy. Acta Chir. Scand., 136:611, 1970.
33. Wastell, C., MacNaughton, J. I., Colin, J. F. and Gleeson, J.: Gastric Secretion and Emptying Before and After Parietal Cell Vagotomy, With and Without Pyloroplasty (abstract). Br. J. Surg., 58:871, 1971.
34. Weber, J., Jr. and Kohatsu, S.: Pacemaker Localization and Electrical Conduction Patterns in the Canine Stomach. Gastroenterology, 59:717, 1970.
35. Werle, J. M., Brody, D. A., Ligon, E. W., Jr., Read, M. R., and Quigley, J. P.: The Mechanics of Gastric Evacuation. Am. J. Physiol., 131:606, 1941
36. Wilbur, B. G. and Kelly, K. A.: The Effect of Gastric Fundectomy on Canine Gastric Pacesetter Potential, Transmural Pressure, and Emptying (abstract). Gastroenterology, 62:863, 1972.

DISCUSSION

DR. LLOYD M. NYHUS (Chicago): The vagus nerves have come a long way since Pavlov. Stimulation of the parietal cell to secrete hydrochloric acid, vagal release of the hormone, gastrin, interrelationship of the vagus and the hormones, secretin, and cholecystokinin and now, the beautiful dissection of the role of the vagus in control of gastric pressure and motility by Wilbur and Kelly.

These studies, confirm by elegant methodology, that preservation of the vagal nerves to the antrum allow normal or near normal function of the antrum and pylorus.

Following proximal gastric vagotomy, cinefluorography in our own patients demonstrates this continued antral function dramatically.

The authors have given us more information. They have differentiated between the regulation of gastric emptying of liquids by the vagally innervated proximal stomach by a transmural pressure system and the emptying of solids by the vagally innervated antrum.

A major cause for concern with the operation of proximal gastric vagotomy is the unknown recurrent ulcer rate.

Is there a danger of vagal re-innervation of a proximal stomach by the nerves of Latarjet left intact to the antrum?

There is no answer to this question. However, Wilbur and Kelly have given to us new and important research tools which may help to answer this tantalizing question.

Finally, have the authors repeated the gastric transmural pressure recordings at longer intervals than 1 month after proximal gastric vagotomy? Longer observation may clarify certain of these important issues.

Dr. Edward Roy Woodward (Gainesville): I had the pleasure of reading the complete manuscript and this is certainly a beautiful demonstration of the role of the vagus in the emptying function of the stomach.

We have been intrigued by the potentialities for the operation of proximal gastric vagotomy for duodenal ulcer and our early results in 15 cases are good. The basal acid output was sharply reduced in nearly all instances and we have been interested in that the stimulated secretion falls very little or none.

Our laboratory evaluation of this procedure has proceeded along somewhat different lines. In the dog we have used a meal of 500 Gm. of blenderized horsemeat introduced into the stomach. We observed that in the control animal the pH in the fasting stomach is 2.4 and the serum gastrin 23 picograms per ml.

There is a definite rise in the serum gastrin with this relatively large meal. We were surprised to find how long it took the normal dog's stomach to empty this semi-solid meal, 7 hours and 15 minutes with a standard error of 1 hour.

After proximal gastric vagotomy, the resting pH in the stomach was essentially the same. However, the serum gastrin level was nearly three times that in the control animal. Even more striking was the very sharp increase in the serum gastrin which followed the introduction of the semi-solid meat meal. The emptying time was essentially the same. Statistically, these figures are not different so that the emptying of the semi-solid meal was not affected by proximal gastric vagotomy.

Dr. James Charles Thompson (Galveston): There are several things brought out by this fine paper. One of them challenges an idea that I, at least, have held, that the duodenum functions as an osmoregulator. Many of our classic ideas about the dumping syndrome have stipulated that anything that either bypasses or destroys the function of the pylorus will lead to dumping because it will allow the rapid passage of hyperosmolar material into the upper small bowel. These studies are the first I know of to directly address that question and to come to the opposite finding.

Secondly, this study provides us with further information on some fascinating bits of knowledge that we are beginning to gather about the effects of various acid-reducing procedures on serum gastrin levels.

Clinically, all reports of operations of vagotomy and emptying procedures in which gastrin measurements have been done show that there is a great postoperative increase in fasting gastrin levels. This has been, I think, usually ascribed to a dimunition in the acid inhibition, the acid feedback mechanism.

Drs. Wilbur and Kelly show us that in this operation at least there is another facet to be considered. There is a significant increase in antral pressure which probably would lead to some distention of the antrum and perhaps further release of gastrin. The coincidence of the two, that is the relatively high pH due to vagal denervation of the parietal cell mass and the increased pressure, would perhaps together be synergistically responsible for the rather high, sometimes doubled, gastrin levels and we and others have found postoperatively in patients with vagotomy and pyloroplasty.

Conversely, our results are somewhat different from those reported by Dr. Woodward in that we do not get stimulated levels of acid secretion.

Lastly, I think, as far as our remarks, this brings us to the question of when we do the operation of proximal gastric vagotomy, should we include an emptying procedure?

When Fritz Hölle in Munich first began his study of this operation, in a few patients he did no antrum procedure and then because of high acid levels and a few recurrences, he adopted pyloroplasty.

As you all know, Dr. Andrup in Copenhagen and Dr. Johnston and Dr. Golligher in England have reported now a rather large series in which their results seem to be quite good in patients in whom a proximal gastric vagotomy without emptying procedure had been performed.

I would agree with Lloyd Nyhus in that I think we have to wait awhile before we are sure this is going to be a safe operation. It would seem to me that now, control trials should be directed as to whether or not a gastric emptying procedure should be included with parietal cell or proximal gastric vagotomy, which, I suspect, will be the operation of the future (with or without an emptying procedure).

Dr. Keith A. Kelly (Closing): Dr. Nyhus, we have not studied the animals longer than the period indicated in our report, but it would be valuable to know if there is any return of vagal function in the proximal stomach after months or years.

Dr. Woodward, the semi-solid meals that you are using must be handled in a similar manner to the solid spheres that we have used, since you did not show any increase in their speed of emptying. Perhaps if you had given your dogs or your patients liquids, you would have found gastric emptying faster.

Dr. Thompson, I do not know whether the increases in transmural pressure that we have shown after proximal gastric vagotomy would result in an increased release of antral gastrin. The increases in pressure are not large, but perhaps they are great enough to augment the output of gastrin.

Our data would support the fact that a procedure designed to increase the speed of gastric emptying is not required with proximal gastric vagotomy. If anything, we have shown that proximal gastric vagotomy speeds rather than slows gastric emptying.

The concept emerging from these experiments is that the proximal and distal parts of the stomach each have separate functions. The proximal stomach accommodates ingesta, relaxes, and keeps transmural pressure low. The distal stomach grinds and mixes.

The vagus has an important regulatory role in both the proximal and distal stomach. When we operate for duodenal ulcer, it is important to divide as few vagal nerves as is consistent with the treatment of the disease.

Measurement of Endogenous Release of Cholecystokinin by Radioimmunoassay

DAVID D. REEDER, M.D., HORST D. BECKER, M.D., NANCY J. SMITH, B.S.,
PHILLIP L. RAYFORD, PH.D., JAMES C. THOMPSON, M.D.

From the Department of Surgery, The University of Texas Medical Branch, Galveston, Texas

THE HORMONE CHOLECYSTOKININ is the principal stimulus for contraction of the gallbladder and for secretion of enzymes and protein by the pancreas. Cholecystokinin activity was discovered in extracts of small bowel mucosa by Ivy and Oldberg[12] in 1928, and the effects on pancreatic secretion were observed by Harper and Raper[9] in 1943. These two independent discoveries led to the concept of two separate hormones, which were designated respectively as cholecystokinin and pancreozymin. It is now agreed that the two are one, and the hormone has been isolated and purified and its amino acid composition has been determined.[15,25] Since the cholecystokinin activity of the hormone was the earlier discovery, Grossman[8] has proposed the term cholecystokinin (CCK) for all actions of this hormone.

Studies on the release, action and degradation of CCK have been hampered by lack of a sensitive and precise method for its measurement. Since CCK is structurally similar to gastrin (the C-terminal 5 amino acid residues are identical), the two hormones share several actions. Furthermore, secretin, another hormone present in small bowel mucosa, may be released at the same time as CCK and their actions may overlap. Specific methods for measurement of each of these hormones are needed to unravel their inter-relationships.

In the present work, we describe the development of a specific radioimmunoassay for measurement of circulating serum levels of CCK in man and levels of CCK in serum and small bowel mucosa in dogs. No cross reactivity with either gastrin or secretin has been demonstrated in the assay. We have measured the effect of the release of endogenous CCK on circulating serum concentrations of CCK in man and in dogs.

Materials and Methods

Technic of Radioimmunoassay of Cholecystokinin (CCK)

Antibodies to purified CCK were prepared by immunizing 11 rabbits. The immunogen used was porcine CCK obtained from Professors E. Jorpes and V. Mutt (Karolinska Institutet, Stockholm) which had a potency of 250 Ivy dog units per milligram (250 IDU/mg.). Immunogen (75 IDU) was dissolved in 1 ml. normal saline, emulsified in 1 ml. Freund's complete adjuvant, and injected subcutaneously into each rabbit at approximately 2-month intervals. Two weeks after the eighth injection, specific anti-CCK activity was found in the serum of one of the 11 rabbits.

Purified CCK (Jorpes), with a potency of 500 IDU/mg., was iodinated to specific activities of 200–250 μC/μg with ^{125}I using the chloramine T method of Greenwood and Hunter.[6] Iodination was performed with 2 mC of carrier free ^{125}I and 5 μg of hormone at pH 6.0. The reaction time was 20 seconds. Iodinated CCK was separated from free iodide components by chromatography using Sephadex G-25 and was eluted with 1 M

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25–27, 1973.

Request reprints: David D. Reeder, M.D., Department of Surgery, University of Texas Medical Branch, Galveston, Texas 77550.

Supported by grants from the National Institute of Health, AM 15241 and RR-00073, and by a grant from the John A. Hartford Foundation, Inc.

A preliminary report of a portion of this work has been published.[21]

NaCl, pH 6.0. The fraction containing iodinated CCK was diluted (with 0.1 M potassium phosphate buffer [pH 7.5] containing 2% normal rabbit serum) to provide 12,000 cpm/100 µl, which was the amount of radioactivity added to each tube in the assay. The labeled hormone is used in the assay system within 24 hours.

The radioimmunoassay system utilizes the double-antibody technic of Odell, Rayford and Ross.[10] The reference standard used is purified porcine CCK (Jorpes) with a potency of 500 IDU/mg. (17% pure). A correction is made in all calculations to reflect 100% purity. Unknown serum specimens were assayed at a 1:3.3 dilution, *i.e.*, 300 µl of the specimen are included in the final incubation mixture of 1.0 ml. The final dilution of the antiserum to CCK is 1:1000. The incubation mixture is allowed to react at 4° C for 6 hours before goat antirabbit serum is added. The mixture is incubated for 12 hours before it is centrifuged. All samples are assayed in duplicate. A standard dose-response curve (from 0.65 to 12.8 nanograms of CCK) is constructed for each assay (Fig. 1). Since final serum dilutions in our assay are 1:3.3, the range of sensitivity is from 1.95 to 48.4 nanograms per ml. (ng/ml.) of serum. Serum samples containing more than 48.4 ng/ml. are reassayed after dilution with 0.5 M phosphate buffer.

Several analogues of CCK[25] in dosages ranging from 1 to 10^5 ng were tested in the radioimmunoassay system to determine their ability to displace iodinated CCK from combination with CCK antibody. The following analogues were tested: the toxic decapeptide, caerulein; the synthetic C-terminal octapeptide of CCK; pentagastrin; synthetic human gastrin I; purified porcine secretin (Jorpes). No significant displacement was observed in these dose ranges, indicating the specificity of the CCK antibody for the CCK molecule.

Postprandial human and canine serum samples were added to the assay system in amounts between 40 and 300 µl. Logarithmic plots of the dose response curves are shown in Figure 1. Analysis of these data by use of a computer program[23] indicates that these dose response curves for serum are parallel to the reference curve for CCK.

The reproducibility of the assay was determined by repeatedly measuring the CCK concentration in samples of the same serum in a single assay, and also by determining variations in measurement of CCK concentrations in identical samples measured in several assays. The CCK concentration in a pool of serum from three healthy men was measured 15 times in one assay; the mean measured CCK concentration (±SD) was 4.29 ± 0.14 ng/ml. Aliquots of a separate pool of serum from different individuals were measured on five separate assays with a resultant mean concentration of 7.2 ± 1.5 ng/ml.

Studies in Man

In five subjects we tested the effect of intravenous injection of purified porcine CCK (0.5 IDU/Kg.) on the measured serum concentrations of CCK. In four different subjects, we measured the effect of a fatty meal on serum CCK concentrations over a 2½ hour period. Serum levels of CCK are expressed as mean values with the corresponding standard error; values are given in ng/ml. Basal values are given as the average of two pre-test samples.

Studies in Dogs

Effect of Application of Acid to the Jejunum: Five dogs were prepared with gastric fistulas and Thiery–Vella loops of the first 50 cm of jejunum. After a 3-week recovery period, a second laparotomy was performed and a polyvinyl catheter was placed into the portal vein via a branch of the splenic vein. Awake dogs were studied in Pavlov stands on the third day after placement of the portal vein catheter. During perfusion of the jejunum with either 0.1 N HCl, 0.9% NaCl or 0.2 N HCl, portal venous serum samples and gastric secretions were collected. Serum concentrations of CCK were measured by radioimmunoassay for CCK, and serum gastrin was measured by a radioimmunoassay for gastrin developed in our laboratory.[14] Output of gastric acid is expressed as milliequivalents per 15 minutes (mEq/15 min.) and was determined by titrating a 1-ml. sample of gastric juice with 0.1 N NaOH (phenol red was used as an indicator).

Effect of Intraduodenal Infusion of Amino Acids: Four dogs were prepared with pancreatic fistulas as described by Herrera and associates,[10] and also with gastric fistulas. The lateral limb of the pancreatic cannula was placed into a small pouch of duodenum containing the opening

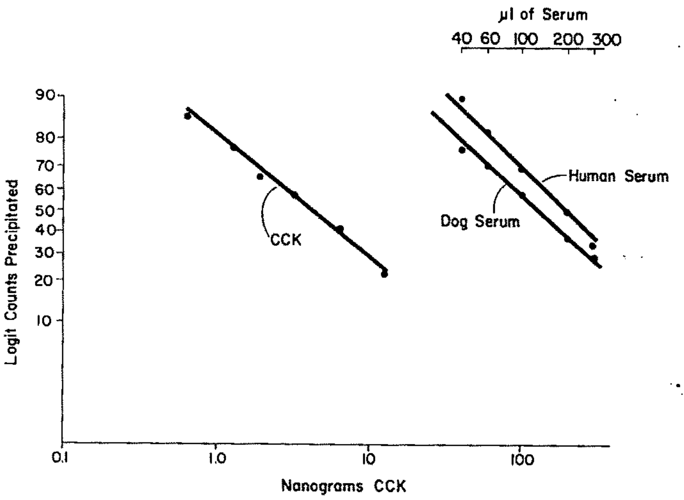


FIG. 1. Radioimmunoassay dose response curves for purified porcine CCK and for human and dog serum. Note separate abscissa scale for serum.

of the major pancreatic duct, allowing collection of pure pancreatic juice. The main limb of the cannula was placed into the duodenum 15 cm. distal to the pylorus. The cannula is constructed to allow collection of pure pancreatic juice during instillation of test substances into the duodenum via a hollow obturator. Studies were performed 3 weeks after operation with the dogs in the fasting state. During instillation into the duodenum of varying doses of a mixture of amino acids, serum samples were obtained from a peripheral vein for radioimmunoassay of CCK. Pancreatic secretions were collected continuously and the concentration of protein in pancreatic juice was determined with a spectrophotometer by measuring absorbance at 280 mμ (compared to a standard solution of human serum albumin). Protein output, expressed as mg./30 min, was determined by adding the two highest consecutive 15-min outputs at a given dose of amino acid solution.

Measurement of Concentrations of CCK in Small Intestinal Mucosa: Three fasting mongrel dogs were anesthetized with pentobarbital sodium. A laparotomy was performed and the following segments of small bowel were excised:

1) proximal duodenum—from pylorus to entrance of main pancreatic duct.
2) distal duodenum—from entrance of main pancreatic duct to the ligament of Treitz.
3) proximal jejunum—initial 30 cm. distal to ligament of Treitz.
4) distal jejunum—a 30 cm. segment immediately proximal to the junction of the proximal ⅓ and distal ⅔ of jejuno-ileum.
5) ileum—a 30 cm. segment taken between 100–300 cm. proximal to the ileocecal valve.

Each segment of bowel was opened along the antimesenteric border. The mucosal surface was rinsed with iced normal saline and the entire mucosa was removed by scraping. A small piece of rectus abdominis muscle was excised to serve as a control tissue. Each tissue was weighed separately, diluted with four parts distilled water, and heated to 95° C for 20 minutes in a water bath. After heating, 500 kallikrein inactivator units of aprotinin (Trasylol) was added to each milliliter of supernatant, and the resultant mixture was assayed for CCK that day. Concentrations are expressed as nanograms of CCK per gram of mucosa (ng/Gm).

In all studies, results are given as either the individual value for each sample or as the mean value with the corresponding standard error of the mean. Significance of differences between means was evaluated by use of the Student "*t*" test; differences with p values less than 0.05 were considered significant.

Results

Studies in Man

Effect of Exogenous CCK on Serum CCK: Five healthy volunteer subjects received an injection of purified porcine CCK (Jorpes), 0.5 IDU/Kg., over a 2-minute period. The mean basal serum concentration of CCK (prior to injection) was 17.8 ± 1.1 ng/ml. (Fig. 2). Five minutes after initiation of the injection, the level rose significantly to a peak of 33.0 ± 2.2 ng/ml. and remained elevated at 10 minutes (29.8 ± 2.4 ng/ml. $p < 0.05$). By 15 minutes, serum CCK had fallen to 23.7 ± 1.6 ng/ml. and by 45 minutes to near baseline, 20.8 ± 1.5 ng/ml.

Effect of a Fatty Meal on Serum CCK: The four subjects ate a fatty meal consisting of 2 fried eggs, 4 slices of bacon, 2 pieces of sausage, 2 slices of buttered toast and a cup of cream. The mean basal serum CCK concentration was 4.8 ± 0.3 ng/ml. (Fig. 3). After the subjects began eating, there was a gradual rise in serum CCK to 8.3 ± 1.1 ng/ml. at 30 minutes and to a peak of 9.1 ± 1.6 ng/ml. at 45 minutes ($p < 0.05$). By 105 minutes, the mean serum CCK value had fallen to 5.5 ± 0.3 ng/ml. At 120 minutes there was a slight increase in CCK to 6.3 ± 0.5 ng/ml.

Studies in Dogs

Effect of Application of Acid to the Jejunum: The protocol followed in these studies with five dogs is shown schematically in Figure 4. A Foley catheter was inserted into the proximal end of the Thiery–Vella fistula, and the balloon was inflated gently to prevent reflux. The jejunal loop was perfused at the rate of 150 ml./hr for three 45-minute periods, first with 0.1 N HCl, then with 0.9% NaCl, and finally with 0.2 N HCl. The mean basal serum CCK value in the portal vein was 111.9 ± 10.2 ng/ml. (Fig. 4). This value rose gradually during perfusion of the jejunal loop with 0.1 N HCl to a peak value of 252.0 ± 65.4 ng/ml. after 45 minutes of perfusion ($p < 0.05$). Acid output from the gastric fistula rose during that period from 1.05 to 3.58 mEq/15 min, presumably reflecting stimulation of gastric secretion by CCK. When the jejunal perfusate was changed to 0.9% NaCl, serum CCK values fell but were still elevated over basal, and acid output fell in a parallel fashion to near basal values. When perfusion of the jejunum was begun with 0.2 N HCl, CCK again increased gradually to 242.1 ± 37.4 ng/ml. after 45 min, and acid rose to 3.39 mEq/15 min. The mean basal serum level of gastrin in the portal vein was 70 ± 9 pg/ml. and there was no significant change throughout the studies (Fig. 4).

Effect of Intraduodenal Infusion of Amino Acids: The protocol for these experiments in four dogs is shown schematically in Figure 5. An equimolar mixture of L-tryptophan and L-phenylalanine (100 mM solution) was adjusted with NaOH to pH 7.0, and mannitol was added to achieve an osmolarity of 300 mOsm/L. This solution was introduced into the duodenum at rates of 0.5, 1, 2, 4 and 8 mM per hour. Each dose level was administered for 1 hour. The gastric fistula was open throughout the study to prevent acid from entering the duodenum. The mean basal serum level of CCK in the four dogs was 18.6 ± 3.4 ng/ml. (Fig. 5). During infusion of the mixture of L-tryptophan and L-phenylalanine at a rate of 0.5 mM/hr, CCK rose significantly to 35.0 ± 5.6 ng/ml. During infusion at rates of 1, 2, 4 and 8 mM/hr, CCK values were respectively 51.2 ± 12.9 ng/ml., 52.4 ± 18.1 ng/ml., 29.6 ± 2.6 ng/ml. and 29.0 ± 2.7 ng/ml. Values significantly higher than basal are identified by asterisks in the figure. Basal pancreatic protein output was 205 ± 48 mg./30 min; this value rose gradually to a peak of 648 ± 55 mg./ 30 min during infusion of the amino acid mixture at the rate of 4 mM/hr.

Concentrations of CCK in small intestinal mucosa: Levels of CCK in the small intestinal mucosal and rectus muscle samples from the three dogs are shown in Table 1. CCK values in the upper small bowel were approximately double those in the ileum. Values obtained from the duodenum were similar to those from the jejunum. The CCK measured in muscle may represent actual sequestration of the hormone or may be due to a non-specific interference with antibody binding.

Discussion

The studies demonstrate direct measurement of CCK release in man after a meal, and in dogs after stimulation of the proximal small bowel. The radioimmunoassay system employed appears to be a suitable method for measurement of basal and stimulated levels of endogenous cholecystokinin. The amino acid sequence for the CCK molecule has been reported recently:[18,25]

Lys-Ala-Pro-Ser-Gly-Arg-Val-
Ser-Met-Ile-Lys-Asn-Leu-Gln-
Ser-Leu-Asp-Pro-Ser-His-Arg-
Ile-Ser-Asp-Arg-Asp-Tyr-Met-
|
SO_3H

Gly-Trp-Met-Asp-Phe-NH_2

Since no significant cross reaction was observed with polypeptides which possess identical C-terminal peptide sequences (gastrin, pentagastrin, caerulein and the C-terminal octapeptide of CCK), the anti-CCK antibody seems to be directed against the proximal portion of the molecule. To date, no radioimmunoassay for CCK has been reported which cross reacts with the C-terminal peptide sequence Trp-Met-Asp-Phe-NH_2 possessed by both gastrin and CCK.[4,5,21,32] Radioimmunoassay technics for gastrin differ; all methods reported for gastrin react with the C-terminal tetrapeptide.

Go and co-workers[5] reported a radioimmunoassay system using antisera to crude porcine CCK. This assay system measured elevated levels of serum CCK in pigs, but did not react with human CCK, which suggests that the structure of porcine CCK differs from that of man. Although our antiserum was produced against porcine CCK, serial dilutions of serum from both man and dogs react in parallel to the porcine CCK standard in the assay system, providing evidence for structural similarity of the proximal CCK molecule among the three species.

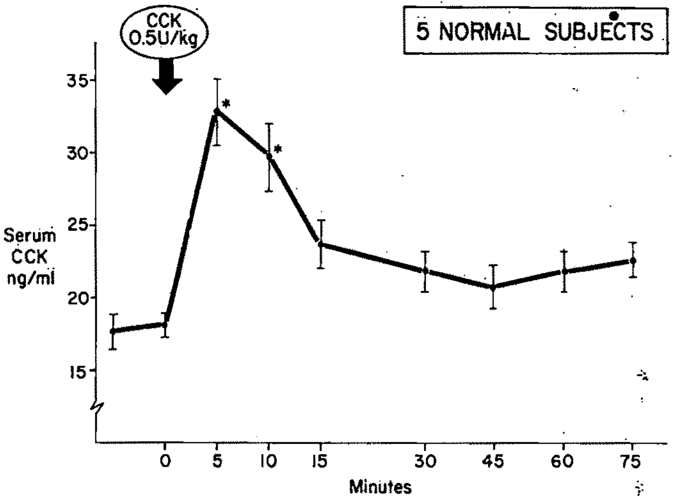


FIG. 2. Effect of an intravenous injection of purified porcine CCK on serum concentrations of CCK (in 5 normal human volunteers) measured by radioimmunoassay. In this and subsequent figures, narrow vertical bars indicate ± one standard error. Asterisks identify values significantly elevated over basal.

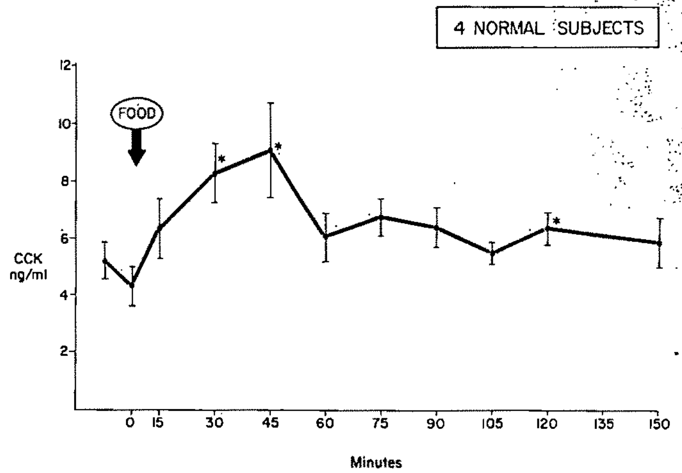


FIG. 3. Effect of a fatty meal on serum concentrations of CCK (in 4 normal human volunteers) measured by radioimmunoassay. Asterisks identify values significantly elevated over basal.

The presently reported values of CCK in human serum and in serum and intestinal mucosal extracts from dogs are based on a reference preparation (CCK, 500 IDU/mg.) that has been measured by bioassay and is only 17% pure.[15] Serum levels of CCK, measured against this standard, are in the range of 5–20 ng/ml., and the upper small bowel mucosa of dogs contains several hundred nanograms per gram of mucosa. The serum levels obtained in man and in dogs in the present study are in agreement with those reported in pigs[5] and in preliminary reports in man.[4,21] Although most polypeptide hormones exist in serum in concentrations of picograms per ml., some have been reported in nanogram per ml. concentrations [*e.g.*, progesterone,[3] human growth hormone,[11,31] and luteinizing hormone[20]].

Although it is widely agreed[2] that serum concentrations of gastrin in man are in the range of 20–150 pg/ml. (using 17 amino-acid gastrin as the standard), it is now known that there are at least three forms of gastrin in the circulation that are immunochemically indistinguishable (17 amino-acid gastrin, 33 amino-acid gastrin, and big-big gastrin) and that the major component of circulating gastrin is not the 17 amino acid form.[7,27,28,30] No radioimmunoassay for gastrin has been developed using the larger forms of circulating gastrin as either antigen or as standard, so the individual concentrations of the various forms of circulating gastrin are unknown. In light of this information, certain potential limitations of the technic for measurement of CCK should be recognized: the molecular form or weight of circulating CCK is unknown, the reference standard is *porcine* CCK, and the standard is only 17% pure. Although the values reported for CCK concentrations may not be absolute, measurement by radioimmunoassay nonetheless allows a concept of quantitation and does not detract from the validity of measured *changes* in relative CCK concentrations during physiologic studies. After intravenous injection of purified porcine CGK into human volunteers (Fig. 2), we measured an abrupt rise in circulating CCK from a basal level of 17.8 ng/ml to a peak of 33.0 ng/ml. The magnitude of this increase in CCK concentrations is greater than would be anticipated with the dose of CCK that was given. There are several possible explanations for this apparent discrepancy. The CCK preparation that was administered intravenously was less pure than the preparation used as a standard, and perhaps some of the biologically inactive polypeptides in the less pure preparation are bound by the anti-CCK antiserum in the radioimmunoassay system. This could lead to discrepancies between the biologic and immunologic measurements of CCK; such discrepancies have been reported for other peptide hormones.[19a]

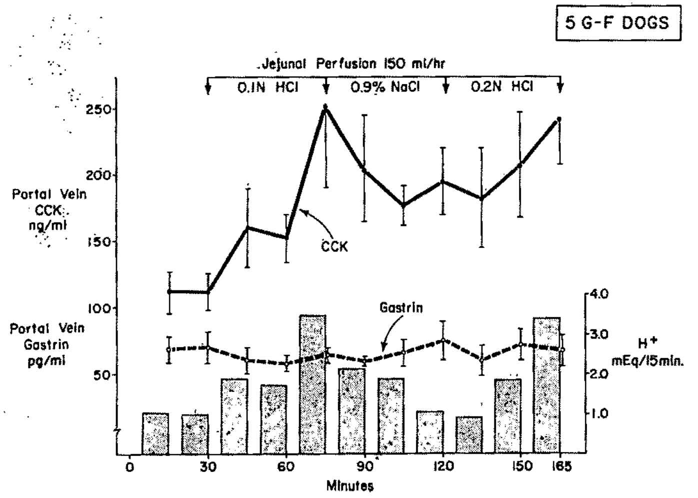


FIG. 4. Effect of perfusion of a Thiery-Vella loop of jejunum with acid or saline on portal serum CCK and gastrin (measured by radioimmunoassay) in 5 dogs. The bar graph at the bottom and the ordinate on the right refer to output of gastric acid.

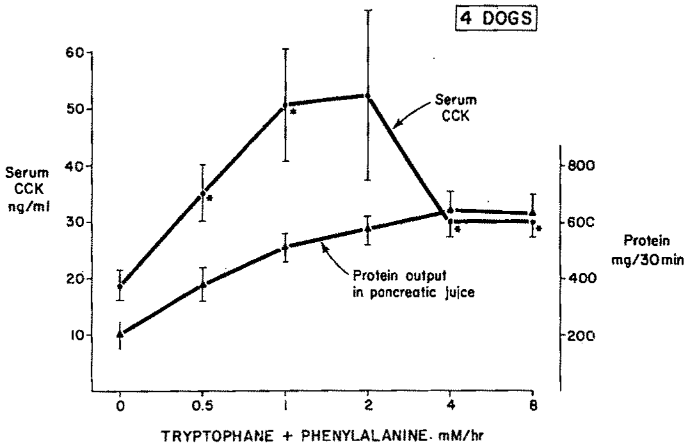


FIG. 5. Effect of intraduodenal infusion of increasing doses of an amino acid mixture into the duodenum in 4 dogs with chronic pancreatic fistulas. The mixture of amino acids was infused for one hour at each dose level. Asterisks identify serum CCK values significantly elevated over basal.

The studies in dogs were performed to correlate CCK release measured by radioimmunoassay with CCK activity measured by bioassay. Since application of acid or essential L-amino acids to small bowel mucosa is known also to release endogenous secretin,[16,17] the physiologic effects measured in the bioassay preparation reflect influence of both of these hormones. Because of overlap-

TABLE 1. *Concentrations of CCK (Ng/Gm. of tissue)*

	Dog#			
	1	2	3	Mean
Duodenum, proximal	251	554	251	353
distal	389	667	511	522
Jejunum, proximal	480	480	320	427
distal	410	347	389	382
Ileum	128	179	125	144
Muscle	43	40	85	56

ping physiologic actions, the specific contribution of each hormone will become known only when precise assay of each is possible. The recent preliminary report of a radioimmunoassay for secretin[24] suggests that this possibility is imminent.

The concentration of immunoreactive CCK in duodenal and jejunal mucosa was small compared with levels of gastrin in antral mucosa.[13] The ratio of antral gastrin concentration to duodeno-jejunal CCK concentration in dogs is approximately 10,000 ng/Gm. to 400 ng/Gm., or 25 to 1; the mass of duodeno-jejunal mucosa in dogs is 11 times greater than antral mucosa.[26] The ratio of serum gastrin concentration to serum CCK concentration in dogs is approximately 80 pg/ml. to 20,000 pg/ml. or 1 to 250. Therefore, compared to gastrin, there would appear to be much less CCK available in mucosa to maintain a much higher concentration of CCK in serum. Although these ratios are clearly rough approximations, they suggest different rates of metabolism of the two hormones. Since the biologic half-life of endogenous CCK [by bioassay[1]] and exogenous CCK (Fig. 2) appear to be similar to that of gastrin,[22,29] the difference may be in the rate of synthesis or in the size of the fraction synthesized that is stored in mucosa.

Summary

We have developed a radioimmunoassay technic for measurement of circulating levels of endogenous CCK in man and in dogs. There is no cross reaction with gastrin. Using this assay, we have demonstrated increases in serum concentrations of CCK following a fatty meal in man, and during application of acid or an amino acid mixture to small bowel mucosa in dogs. Measured concentrations of CCK in small bowel mucosa showed approximately equal concentrations in duodenum and jejunum, which were significantly higher than those in ileum. This radioimmunoassay for CCK should prove useful in delineating the overlapping actions of the gastrointestinal hormones in physiologic studies.

Acknowledgment

We want to thank Professor Stanislaw J. Konturek for his valuable advice and assistance in the performance of the physiologic studies.

References

1. Berry, H. and Flower, R. J.: The Assay of Endogenous Cholecystokinin and Factors Influencing its Release in the Dog and Cat. Gastroenterology, 60:409, 1971.
2. Berson, S. A. and Yalow, R. S.: Radioimmunoassay in Gastroenterology. Gastroenterology, 62:1061, 1972.
3. deVilla, G. O., Jr., Roberts, K., Wiest, W. G., Mikhail, G. and Flickinger, G.: A Specific Radioimmunoassay for Plasma Progesterone. J. Clin. Endocrinol. Metab., 35:458, 1972.
4. Englert, E., Jr., Radioimmunoassay (RIA) of Cholecystokinin (CCK). Clin. Res., 21:297, 1973.
5. Go, V. L. W., Ryan, R. J. and Summerskill, W. H. J.: Radioimmunoassay of Porcine Cholecystokinin-Pancreozymin. J. Lab. Clin. Med., 77:684, 1971.
6. Greenwood, F. C., Hunter, W. M., and Glover, J. S.: Preparation of ^{131}I-Labeled Human Growth Hormone of High Specific Radioactivity. Biochem. J., 89:114, 1963.
7. Gregory, R. A. and Tracy, H. J.: Isolation of Two "Big Gastrins" from Zollinger-Ellison Tumor Tissue. Lancet, 2:797, 1972.
8. Grossman, M. I.: Proposal: Use the Term Cholecystokinin in Place of Cholecystokinin-Pancreozymin. Gastroenterology, 58:128, 1970.
9. Harper, A. A. and Raper, H. S.: Pancreozymin, A Stimulant of the Secretion of Pancreatic Enzymes in Extracts of the Small Intestine. J. Physiol., 102:115, 1943.
10. Herrera, F., Remp, D. R., Tsukamoto, M., Woodward, E. R., and Dragstedt, L. R.: A New Cannula for the Study of Pancreatic Function. J. Appl. Physiol., 25:207, 1968.
11. Hunter, W. M. and Greenwood, F. C.: A Radio-Immunoelectrophoretic Assay for Human Growth Hormone. Biochem. J., 91:43, 1964.
12. Ivy, A, C. and Oldberg, E.: A Hormone Mechanism for Gallbladder Contraction and Evacuation. Am. J. Physiol., 86: 599, 1928.
13. Jackson, B. M., Reeder, D. D., Searcy, J. R., Watson, L. C., Hirose, F. M., and Thompson, J. C.: Correlation of the Surface pH, Histology and Gastrin Concentration of Gastric Mucosa. Ann. Surg., 176:727, 1972.
14. Jackson, B. M., Reeder, D. D. and Thompson, J. C.: Dynamic Characteristics of Gastrin Release. Am. J. Surg., 123:137, 1972.
15. Jorpes, J. E.: The Isolation and Chemistry of Secretin and Cholecystokinin. Gastroenterology, 55:157, 1968.
16. Konturek, S. J., Tasler, J. and Obtulowicz, W.: Localization of Secretin Release by Acid in Small Intestine of the Dog. Am. J. Physiol., 220:124, 1971.
17. Meyer, J. H., Way, L. W. and Grossman, M. I.: Pancreatic Response to Acidification of Various Lengths of Proximal Intestine in the Dog. Am. J. Physiol., 218:971, 1970.
18. Mutt, V. and Jorpes, J. E.: Hormonal Polypeptides of the Upper Intestine. Agenda Papers of the Meeting of The Biochemical Society, University of Sussex, Falmer, England. 2–3 September 1971.
19. Odell, W. D., Rayford, P. L. and Ross, G. T.: Simplified, Partially Automated Method for Radioimmunoassay of Human Thyroid-Stimulating, Growth, Luteinizing and Follicle-Stimulating Hormones. J. Lab. Clin. Med., 70:973, 1967.
19a. Odell, W. D. and Ross, G. T.: Correlation of Bioassay and Immunoassay Potencies for FSH, LH, TSH, and HCG, in Odell, W. D. and Daughaday, W. H. (ed.): Principles of Competitive Protein Binding Assays. Philadelphia, J. B. Lippincott and Company, 1971, pp. 401–413.
20. Odell, W. D., Ross, G. T., and Rayford, P. L.: Radioimmunoassay for Human Luteinizing Hormone. Metabolism, 15:287, 1966.
21. Reeder, D. D., Becker, H. D., Smith, N. J., Rayford, P. L. and Thompson, J. C.: Radioimmunoassay of Cholecystokinin. Surg. Forum, 23:361, 1972.
22. Reeder, D. D., Jackson, B. M., Brandt, E. N., Jr., and Thompson, J. C.: Rate and Pattern of Disappearance of Exogenous Gastrin in Dogs. Am. J. Physiol., 222:1571, 1972.
23. Rodbard, D.: Statistical Aspects of Radioimmunoassays, in Odell, W. D. and Daughaday, W. H. (ed.): Principles of Competitive Protein Binding Assays. Philadelphia, J. B. Lippincott and Company, 1971, pp. 204–259.

24. Teale, J. D., Buchanan, K. D. and Harper, G.: A Radioimmunoassay for Secretin Using Antibodies Raised to Pure Natural and Synthetic Hormone. Gut, 13:849, 1972.
25. Thompson, J. C.: Chemical Structures and Biological Actions of Gastrin, Cholecystokinin, and Related Compounds. In: The International Encyclopedia of Pharmacology and Therapeutics, Pergamon Press Limited. Oxford. Chapter 7, pp. 251–283.
26. Watson, L. C., Reeder, D. D. and Thompson, J. C.: Gastrin Content in the Gastrointestinal Mucosa in Dogs. Submitted for Publication.
27. Yalow, R. S. and Berson, S. A.: And Now, "Big-Big" Gastrin. Biochem. Biophys. Res. Commun., 48:391, 1972.
28. Yalow, R. S. and Berson, S. A.: Further Studies on the Nature of Immunoreactive Gastrin in Human Plasma. Gastroenterology, 60:203, 1971.
29. Yalow, R. S. and Berson, S. A.: Radioimmunoassay of Gastrin. Gastroenterology, 58:1, 1970.
30. Yalow, R. S. and Berson, S. A.: Size and Charge Distinctions between Endogenous Human Plasma Gastrin in Peripheral Blood and Heptadecapeptide Gastrins. Gastroenterology, 58:609, 1970.
31. Yen, S. S. C., Samaan, N. and Pearson, O. H.: Growth Hormone Levels in Pregnancy. J. Clin. Endocrinol. Metab., 27:1341, 1967.
32. Young, J. D., Lazarus, L., and Chisholm, D. J.: Radioimmunoassay of Pancreozymin Cholecystokinin in Human Serum. J. Nucl. Med., 10:743, 1969.

DISCUSSION

DR. JOHN PHILIP SANDBLOM (Lausanne): I should like to congratulate the authors on a beautifully scientific and very successful trial in developing immunoassay methods to follow the formation and release of cholecystokinin.

I should just like to express the nostalgic feelings I have about this subject because it was the object of my first scientific research going back 40 years ago, the research which first brought me an invitation to the United States, which touched on this subject with a very elemental and simple method that one could use for this purpose in a Provincial Hospital in Sweden.

The discussion in those days related to which of the two methods and so forth after gastric resection was the best—the gastroduodenostomy or gastrojejunostomy, the Billroth I or Billroth II. I had the idea that perhaps one could get some information by studying the gallbladder function to find out whether or not there was a difference if a duodenal passage of the chyme was excluded.

So, in a series of patients who were undergoing either of the two operations, I examined the gallbladder function before operation, after operation and later on. The results showed that it did not make any difference whether the chyme passed through the duodenum or not; both after Billroth I and Billroth II, the gallbladder function was equally good. So it could not be used as an argument for either one of those operations from this point of view.

This slide which is now exactly 40 years old, shows the gallbladder emptying before operation, after a meal of egg yolk and the gallbladder emptying after 45 minutes.

In all our patients the gall bladder increased in size after the operation, presumably due to the lack of stimulation for emptying during the fasting period immediately following the operation.

A delay of gall bladder contraction occurred with both methods but it was entirely related to gastric retention and not to duodenal passage.

Typically there was a faint contraction when the patient swallowed the egg-yolk, probably a nervous reflex, but no further emptying until the contrast mixed with egg-yolk appeared in the duodenum or the jejunum. The delay was abolished when the gastric emptying returned to normal, generally in a few weeks—or immediately, if the contrast meal was diluted and could be made to pass right down.

The authors tell about a patient where they tested the release of cholecystokinin after giving olive oil and there was a one hour delay. I would like to ask them if they think it's possible that this delay was due only to the delay in emptying of the stomach.

DR. JAMES C. THOMPSON (Closing): There are some specific areas in which this assay will be valuable. We are now dealing with a group of gastrointestinal hormones in which their activities overlap. We have a whole family of hormones, glucagon-like hormones, glucagon from the pancreas, glucagon from the gut, secretin, material called VIP—vaso-inhibitory polypeptide and a gastric inhibitory polypeptide, as well as the classic hormones of gastrin and cholecystokinin.

Cholecystokinin and gastrin overlap in at least three areas, perhaps four: in gastric secretion, choleresis and in the stimulation of pancreatic secretion, and there is a slight action of gastrin in stimulation of gallbladder contraction.

CCK and secretin overlap in stimulating pancreatic secretion. Although we think classically of secretin as stimulating water and bicarbonate secretion and CCK as stimulating protein, in fact, they have a significant overlap in that they both stimulate both types of secretion.

Lastly, we know that gastrin and secretin have interactions in that secretin inhibits gastrin-stimulated gastric secretion. Up until this point, we have had a method for measuring only gastrin and that assay, in most laboratories, cross-reacts with CCK, although the degree of cross reactivity is small in our hands. Our gastrin assay reacts with CCK in only one part in a thousand, but we are tricked in this by nature. If you noticed on the slides the normal levels of CCK are a thousand times greater than gastrin; that is, our normal levels in man for gastrin are between 80–100 picograms per ml. and in this assay for CCK our levels were between 8 and 20 nanograms. A nanogram is a thousand times a picogram, so that even though the degree of cross reactivity is small, there is so much more circulating CCK that I believe that most gastrin immunoassays do pick up a significant amount of CCK in circulation.

Another object of some interest to us is the difference in concentrations in serum and in mucosa. In antrum mucosa the main source of gastrin, the amount of gastrin in mucosa is a thousand times greater than the mucosal concentrations of CCK we report today even though the amounts in circulation are only 1/1000 that of CCK. This suggests that there are probably significant differences in the metabolic rate for the two hormones.

Superiority of Antiperistaltic Jejunal Segments in Management of Severe Dumping Syndrome

JOHN L. SAWYERS, M.D., J. LYNWOOD HERRINGTON, JR., M.D.

THE DUMPING SYNDROME with its characteristic gastrointestinal and vasomotor disturbances is the most common postprandial complaint after definitive operation for complications of gastrointestinal ulcer disease. Dumping symptoms occur after a part of the stomach is sacrificed and is lost as a storage organ, and from alteration or removal of the pyloric emptying mechanism. The physiologic effects resulting from these aberrations were described by Mix[8] in 1922.

Unfortunately many different postgastrectomy disorders have been erroneously labeled dumping syndrome. In this report we are discussing only patients with early postprandial dumping syndrome. Woodward[15] has made the plea that this entity be carefully delineated from other postgastrectomy disorders by an accurate history. Symptoms of vasomotor imbalance manifested by weakness, faintness with an intense desire to lie down, palpitation, pallor and profuse perspiration are dominant while the gastrointestinal symptoms of postprandial cramping, abdominal pain and urgent diarrhea are less prominent. Ingestion of carbohydrates, especially sweet liquids, initiate these symptoms which are similar to the effects experienced by patients having an insulin reaction.

Most patients suffering from the dumping syndrome have mild, transitory symptoms. Dumping of mild to moderate degree may be fairly well controlled by dietary measures which limit carbohydrates and restrict fluid intake with meals. However, a few patients, less than one per cent in our experience, have severe dumping symptoms with resultant excessive weight loss, anemia, weakness, abdominal discomfort and occasionally uncontrollable diarrhea. When restrictive dietary measures with intensive supportive treatment in the hospital fail to relieve these incapacitating symptoms, serious consideration should be given to remedial operation to prevent the patient from a life of invalidism.

From the Department of Surgery, Vanderbilt University and Surgical Services of Nashville Metropolitan General and St. Thomas Hospitals, Nashville, Tennessee

During the past 12 years, we have utilized three different remedial operations in the treatment of severe intractable dumping syndrome. This report compares the effectiveness of the isoperistaltic single jejunal segment, the double jejunal limb pouch, and the antiperistaltic single jejunal segment interposed between the gastric pouch and duodenum.

Isoperistaltic Jejunal Segment

Schoemaker of the Hague is credited by Hedenstedt[1] with being the first surgeon to interpose an isoperistaltic jejunal segment after gastric surgery in 1911. Henley[3] has reported extensive use of an interposed isoperistaltic jejunal segment between the gastric pouch and duodenum for correction of postgastrectomy syndrome in more than 300 patients. All patients improved including those with early postprandial dumping. Krause[6] and Hedenstedt[2] have emphasized the importance of adding vagotomy when using an isoperistalic jejunal segment to prevent ulceration in the jejunal segment which occurred in 17 per cent of Henley's series of 100 patients with duodenal ulcers who had received primary interpositions of jejunum at the time of the original gastrectomy.

We have used a single interposed jejunal segment

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25–27, 1973.

Reprint request: Dr. John L. Sawyers, Nashville Metropolitan General Hospital, Nashville, Tennessee 37210.

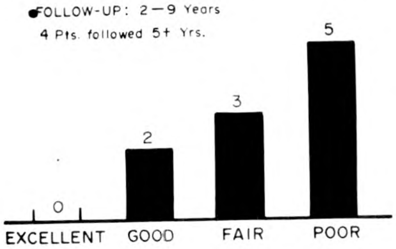


Fig. 1. Results—using isoperistaltic jejunal segment for dumping syndrome.

for patients with afferent-loop syndrome as well as in patients with dumping syndrome. The results in patients with afferent-loop syndrome have been very successful, but the results in patients with early postprandial dumping syndrome have been disappointing.

Ten patients have undergone isoperistaltic jejunal interposition (Henley loop) operation as a remedial procedure for symptoms of the dumping syndrome. There were five men and five women. The ages ranged from 39 to 60 years; most of the patients were in the fifth decade of life. The interval between the original operation and the remedial surgery varied from 2 to 17 years. Three patients previously had undergone an estimated two-thirds distal gastrectomy as the original operation, six patients had undergone vagotomy and a modest resection, and one patient had a vagotomy and pyloroplasty. In the three patients who had two-thirds gastric resection originally, a bilateral truncal vagotomy was done at the time of the Henley loop operation. This procedure is most important to prevent ulceration in the isoperistaltic segment. The patient with pyloroplasty had the antrum excised when the Henley loop was constructed.

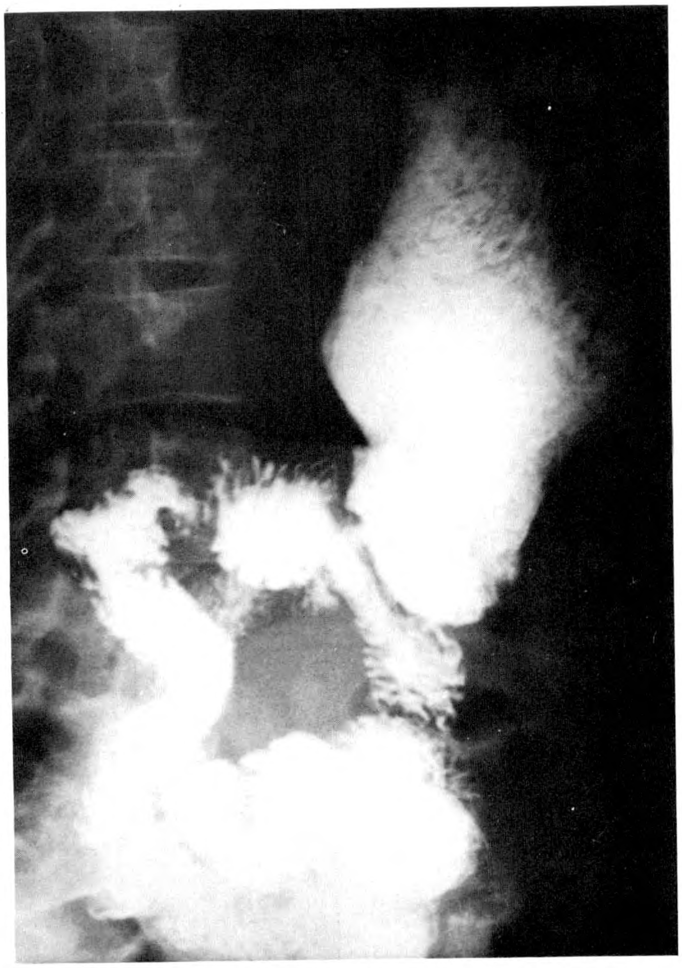


Fig. 2. Patient with isoperistaltic jejunal segment developed kinking of the Henley loop at the gastro-jejunal anastomosis and dilatation of the gastric pouch. The interposed jejunal segment was removed.

One patient has been followed 9 years, two patients for 8 years, one for 5 years, one for 4 years, three for 3 years, and one for 2 years. One patient died at home approximately 2 months following operation.

There have been no excellent results obtained in the group of 10 patients (Fig. 1). Five patients, however, have noted a definite improvement in their dumping symptoms but have not been completely relieved. Two of five patients have gained weight and are judged to have a good result. The other three are considered to have fair results. Five patients had poor results. Three are being maintained on a medical regimen for the dumping symptoms, but are severely incapacitated. There was no further weight loss in these three patients and no other operation has been done.

A fourth patient was a complete failure as she developed obstruction of the Henley loop, and it had to be removed. In 1965, this 39-year-old patient underwent vagotomy and estimated 50 per cent distal gastrectomy with a Billroth II type reconstruction. She developed marked dumping symptoms and had a 25-pound weight loss. Five years later she underwent a take-down of the Billroth II anastomosis and interposition of 15 cm. jejunal segment between the gastric pouch and duodenum. The patient improved for 2 years, but the result was not excellent. At the end of this time she developed nausea, vomiting, and symptoms of high intestinal obstruction. Gastrointestinal X-ray series revealed distention of the gastric remnant and obstruction at the site of anastomosis of the stomach to the jejunum (Fig. 2). She had no free acid in the gastric pouch. At reoperation there was kinking at the proximal end of the loop with no evidence of ulceration. The jejunal segment was removed, and intestinal continuity established by an end-to-end gastroduodenostomy. She improved slightly, but has not regained her lost weight and still has moderate dumping symptoms.

The tenth patient, a 42-year-old woman, also had unsuccessful results. She underwent a 75% resection with vagotomy in 1966. She lost 60 pounds, became

TABLE 1. *Double Limb Jejunal Pouch*

Case	Sex	Age	Original Operation	Subsequent Weight Loss	After Remedial Operation Weight Gain	Follow-Up	Result
1.	M	48	80% Res. B II, no vagotomy	85 lb.	60 lb.	12 years	*Excellent
2.	M	48	Truncal vagotomy, Antrectomy, B I	20	10	11 years	Fair
3.	M	59	80% Res. B II	40	20	11 years	°Good
4.	F	49	60% Res. B II	40	Vagotomy done 20	9 years	Good
5.	M	31	Truncal vagotomy, Antrectomy, B I	35	15	10 years	**Poor
6.	M	34	Truncal vagotomy, Antrectomy, B I	20	20	10 years	***Excellent
7.	M	40	Truncal vagotomy, Antrectomy, B II	15	0	7 years	****Fair
8.	M	52	Truncal vagotomy, Antrectomy, B I	50	20	10 years	°°Poor
9.	M	38	Truncal vagotomy, Antrectomy, B I	35	20	10 years	°°°Poor
10.	M	59	70% Res., B II	30	Vagotomy done 40	8 years	Excellent
11.	M	24	80% Res., B II Vagotomy	20	30	4 years	Excellent
12.	M	47	80% Res., B II Vagotomy	20	25	2 years	Good

* No vagotomy
° At 3rd operation transthoracic vagotomy done. Pouch ulcer healed but constricted pouch and subsequent pouch revision performed. Patient now well.
** Pouch ulcer developed, healed with subsequent transthoracic vagotomy, but patient still doing poorly.
*** Died 10 years after remedial operation of unrelated causes.
**** Died 7 years after remedial operation of unrelated causes.
°° Developed pouch dilation, stasis and reoperation necessary—single reversed jejunal segment inserted.
°°° Developed pouch dilation—pouch made smaller.

emaciated and, in 1969, a 15 cm. isoperistaltic segment of jejunum was inserted between the stomach remnant and duodenum. She responded well in the hospital, but there was no improvement over a 2-month follow-up at home. She died from malnutrition and severe mental depression.

Double Jejunal Limb Pouch

A double plicated iso-antiperistaltic jejunal pouch interpolated between the gastric remnant and duodenum, as described by Poth[10], was used in 12 patients. The size of each segment of jejunum was from 10–15 cm. long. The isoperistaltic segment is joined to the gastric remnant, and the antiperistaltic segment is anastomosed to the duodenum. The two segments are then converted into a single receptacle. Ciné fluoroscopy studies show the pouch to empty slowly and in a piecemeal fashion.

The double limb jejunal pouch has been performed on a total of 12 patients (Table 1). There were 11 men and one woman. The ages ranged from 24 to 59 years. The interval between the original operation for duodenal ulcer and the remedial procedure varied from two to 15 years. Six of the 12 patients originally had truncal vagotomy and antrectomy performed for a complication of duodenal ulcer. Two patients had had an estimated 80% distal gastrectomy without vagotomy as their original operation. One patient had had a 60% distal resection without vagotomy; one had an estimated 70% distal gastrectomy without vagotomy; and two patients had an 80% resection with vagotomy as their original operations.

The clinical results using a double limb jejunal pouch in patients with severe dumping syndrome are seen in Figure 3. Follow-up studies in these patients extend from 2 to 12 years and ten patients were followed for more than 5 years.

The original operative procedure for peptic ulcer disease appears to influence the clinical result obtained from using a jejunal pouch. The first patient to have this type of remedial operation originally underwent an 80% distal gastrectomy without vagotomy and has been followed for 12 years with excellent clinical results. In contrast, patient 3 who underwent an 80% gastric resection without vagotomy developed a pouch ulcer 2 years later and was treated with transthoracic vagotomy. Within a period of a few weeks, the pouch ulcer healed, but in doing so constricted the proximal portion of the pouch necessitating a third operation which consisted of revision to make a

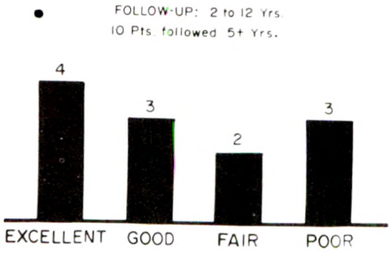


FIG. 3. Results—using double limb jejunal pouch for dumping syndrome.

smaller pouch. This patient obtained an initial poor result because vagotomy was not done, but now he is doing well with an 11-year follow-up.

Patient 5 who underwent initially a truncal vagotomy-antrectomy and a Billroth I reconstruction for ulcer, subsequently had a double limb pouch inserted, but 3 years after insertion the patient developed upper abdominal pain. He had free hydrochloric acid present and in the gastric secretions—20 mEq. over a 12-hour fast and X-rays showed the presence of a pouch ulcer (Fig. 4). The patient underwent transthoracic vagotomy and the ulcer completely healed as demonstrated by X-ray study. The pain has been relieved, but the patient continues to complain of upper abdominal discomfort and fullness and must be considered a failure. He has undergone follow-up study for 10 years. Another failure resulted in patient 8 who did well for 7 years after insertion of a double limb pouch, but then developed progressive upper abdominal fullness, nausea and vomiting. X-ray examination showed the pouch to be dilated and sacculated (Fig. 5). No ulceration was noted in the pouch. The pouch was revised to leave only a short antiperistaltic segment between the remaining stomach and duodenum. This patient is now doing well.

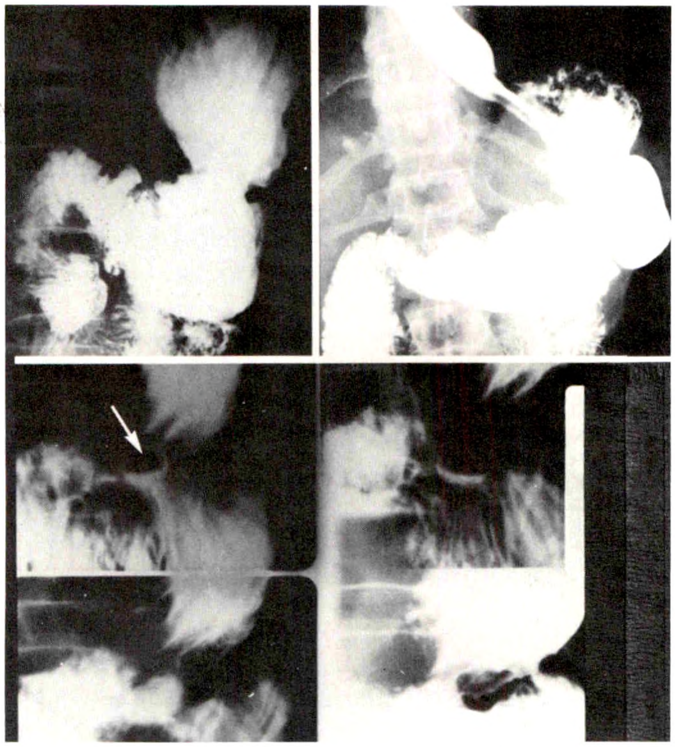


FIG. 4A. Patient with double limb jejunal pouch developed ulcer in pouch (arrow) 3 years after remedial operation.

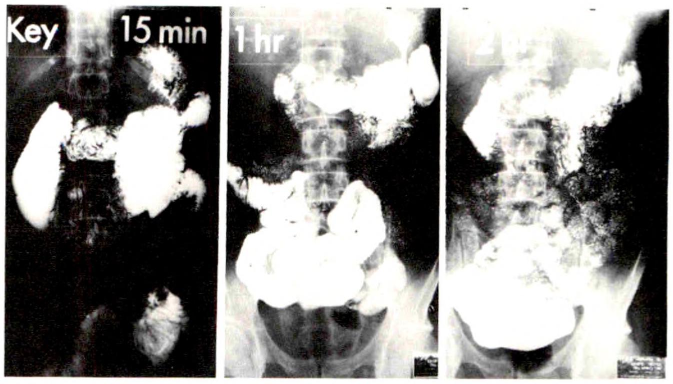


FIG. 4B. Following transthoracic vagotomy, pouch ulcer healed with residual narrowing. Because of abdominal discomfort and fullness, patient is considered to have poor result.

Patient 9 is considered a poor result. This man gained weight and did well for 5 years after insertion of the pouch, but then noted progressive upper abdominal discomfort and bloating which became progressively worse. This was followed by infrequent nausea and vomiting, which increased to the point that the patient vomited every day. The vomitus contained the food which he had eaten the day before. X-ray studies revealed no evidence of a pouch ulcer, but the pouch was very dilated, sacculated, and emptied poorly (Fig. 6). The pouch was revised and made smaller. Over a 6-month period this patient has gained 20 pounds and has been relieved of his difficulty.

The results are deemed fair in two patients (Cases 2 and 7) who continue to experience a rather marked amount of upper abdominal discomfort and occasional nausea and vomiting. They each, however, state that they are improved over their preoperative status.

Antiperistaltic Jejunal Segment

A single antiperistaltic jejunal segment interposed between the gastric remnant and duodenum for management of the dumping syndrome was advocated by Poth[9] in 1957 and reported by Schlicke[13] in 1963. The reversed segment prolonged gastric pouch emptying without causing obstruction. Schlicke[13] and later Sanders[12] added vagotomy when using the antiperistaltic segment and reported no obstructive phenomena. Each surgeon reported marked improvement in his patients. Reversed jejunal segments have also been used to treat dumping following Billroth II gastrojejunostomy without routing food into the duodenum. Jordan[4] reported success with this method in 1963.

During the past 11 years, we have used a single antiperistaltic jejunal segment placed between the stomach and duodenum to treat intractable dumping symptoms in 28 patients. There were 21 men and eight women with an age range from 26 to 62 years. In 23 patients the original operation for duodenal ulcer was truncal vagotomy and gastric resection removing from 40 to 75% of the distal stomach. One patient had a 70% gastrectomy without vagotomy, and four patients had truncal vagotomy and pyloroplasty. The interval between the original operation and remedial surgery was from 1 to 15 years. Each patient was severely incapacitated with early postprandial dumping symptoms. Weight loss ranged from 20 to 70 pounds with an average loss of 30 pounds. Approximately one-half of the patients complained of explosive diarrhea initiated by eating. The results are shown in Figure 7. Twenty patients have obtained excellent results. These patients have either regained back to their ideal weight or to within 10 pounds of their ideal weight. Six patients have been improved by their remedial operation and are judged to have good results. These patients occasionally experience intermittent upper abdominal discomfort and complain of vasomotor symptoms of mild to moderate degree when challenged with a high carbohydrate diet. One patient is considered a fair result. He is improved but bothered significantly by epigastric fullness after eating. He has undergone the shortest follow-up period, 6 months. The other patients have been studied from 1 to 11 years and 14 patients have undergone more than 5 years of follow-up study. One patient died of a coronary thrombosis 3 years after remedial operation. All the other patients are living.

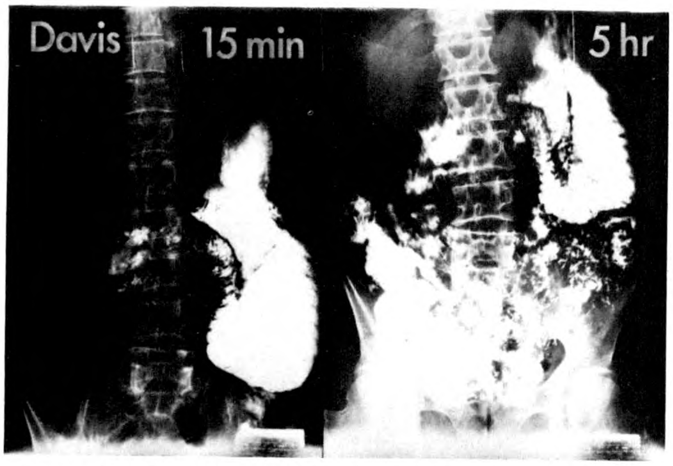


FIG. 5A. Double limb jejunal pouch functioned well for 7 years then became dilated and sacculated. Patient developed progressive upper abdominal fullness, nausea, and vomiting.

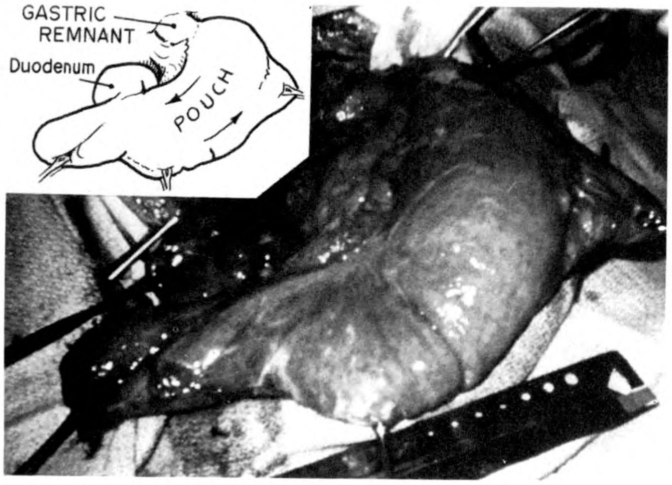


FIG. 5B. Dilated jejunal pouch at reoperation.

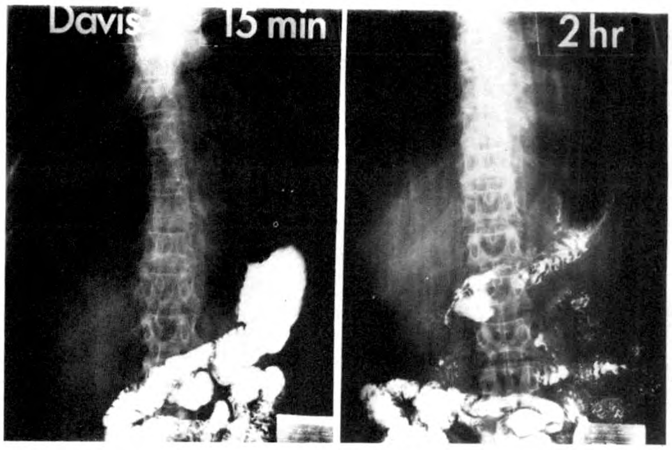


FIG. 5C. After revision of pouch to leave short antiperistaltic jejunal segment, patient did well.

In one patient there was complete failure because of multiple ulcerations in her jejunal limb which was fashioned 18 cm. long. She underwent original operation, a vagotomy and gastric resection, in 1958. Over the next few years she lost 25 pounds, experienced severe vasomotor symptoms of early dumping, and in 1965 she had an 18 cm. reversed jejunal segment interpolated between the gastric remnant and duodenum. This patient did well until 1969, when she began to develop upper abdominal fullness, nausea and vomiting which increased. In 1971, X-rays showed multiple ulcers in the jejunal segment with stenosis (Fig. 8). The jejunal segment was removed and a shorter (8 cm.) segment was interpolated, after which the patient gained 30 pounds. She has been studied almost 3 years and now has an excellent result.

One patient is of unusual interest. This man originally had truncal vagotomy and pyloroplasty performed. He developed severe dumping symptoms and later underwent antrectomy with Billroth I gastrodu-

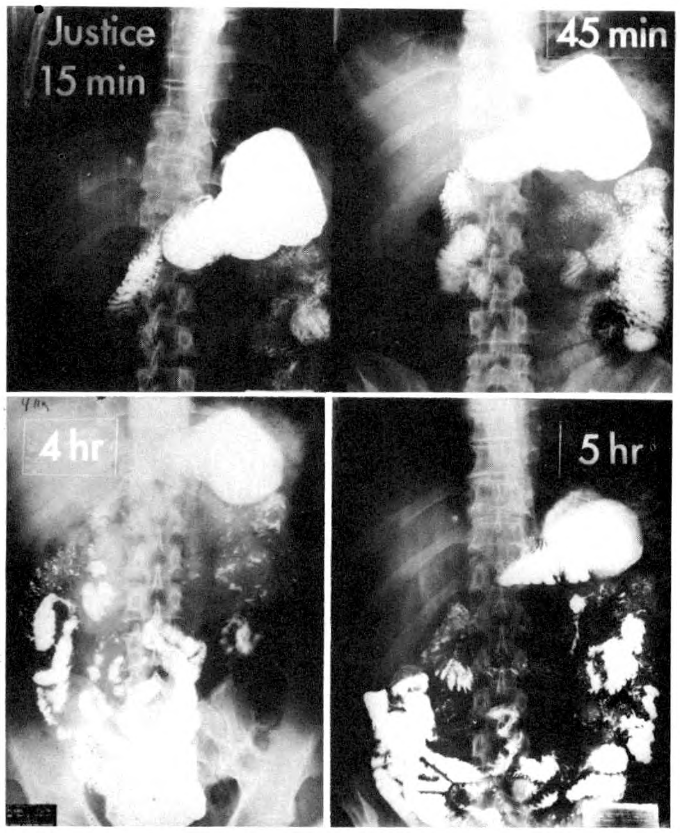


FIG. 6A. After 6 years this patient's double limb jejunal pouch became dilated, sacculated and emptied poorly.

odenostomy. There was no improvement after this operation and the patient went to London where Francis Austin Henley inserted an isoperistaltic jejunal segment between the gastric remnant and duodenum. Dumping symptoms persisted. When he was referred to us, we merely reversed the Henley isoperistaltic segment. He is now considered to have a good result.

Discussion

Remedial operations for treatment of dumping syndrome should be proposed only after all methods of conservative management have failed. Only patients who continue to have severe, intractable dumping symptoms while in the hospital on strict dietary regimens have been subjected to remedial surgery. In most instances, several years have elapsed between the original procedure and reoperation to correct dumping symptoms.

Remedial operation to alleviate dumping symptoms is designed to restore the reservoir function of the stomach and to prolong gastric emptying time. Loss of a normal functioning pylorus, with its valve-like mechanism to slow gastric emptying, appears to be the basic problem in severe, intractable early postprandial dumping syndrome.

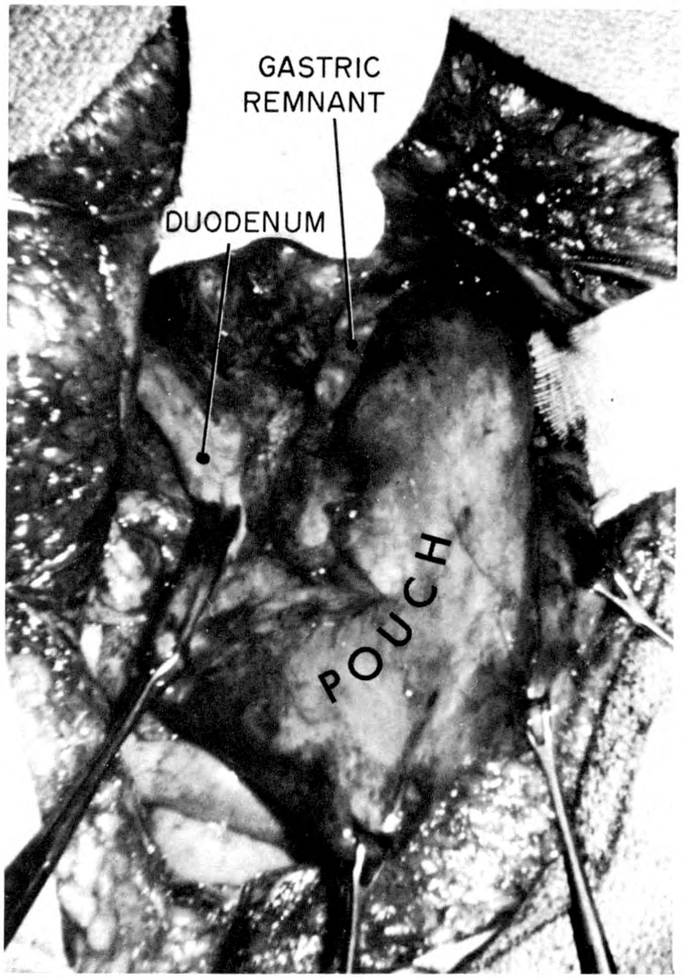


FIG. 6B. Very dilated jejunal pouch at reoperation.

In our experience, a 10 cm. reversed jejunal segment will effectively prolong the emptying time of the stomach without obstruction. Restoration of gastric reservoir function and prolongation of gastric emptying time relieve the severe vasomotor and gastrointestinal symptoms of dumping. The length of the antiperistaltic segment is critical. Experience with an 18 cm. reversed segment resulted in ulcerations and stenosis in the segment which necessitated its removal. Jordan[5] reports unsatisfactory results with 6 cm. reversed jejunal segments. When he used segments of 10 cm., his patients achieved satisfactory results.

We have seen no obstruction occur from use of 10 cm. antiperistaltic segments, yet these reverse segments serve to delay gastric emptying by functioning as a substitute pylorus. Cinéroentgenographic studies have been obtained at various time intervals in the follow-up period and show that reversed segments function effectively as long as 10 years. As the antiperistaltic jejunal segment begins to fill from the gastric remnant, contraction occurs and much of the barium meal in

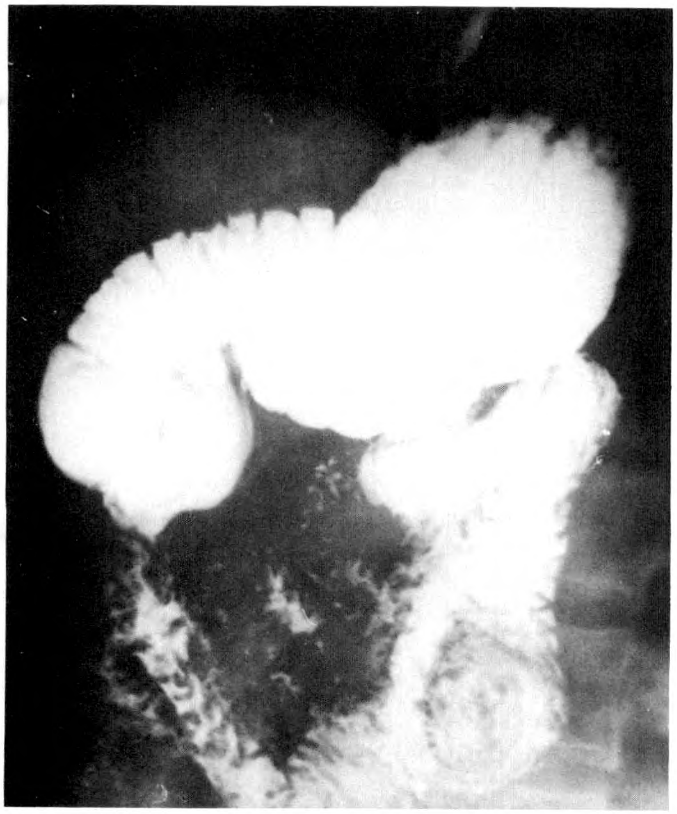


Fig. 6C. After revision to make jejunal pouch smaller, patient's stomach emptied well. He was relieved of abdominal fullness and vomiting.

the jejunal segment refluxes into the gastric pouch. Only a small portion of the meal enters from the segment into the duodenum. A meal, therefore, leaves the gastric pouch in small increments as it did before the integrity of the pylorus was violated (Fig. 9). Symptoms of alkaline or bile reflux into the gastric pouch have not been a problem in our patients, but one patient who volunteered to undergo gastroscopy examination, 6 years after insertion of a reversed jejunal segment, had bile present in the gastric pouch. The gastroscope was passed with ease into the jejunal segment which appeared to have normal mucosa and peristalsis.

We are unable to explain the good results reported by others using an isoperistaltic jejunal segment. While

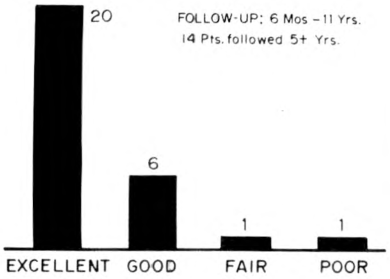


Fig. 7. Results—using antiperistaltic jejunal segment for dumping syndrome.

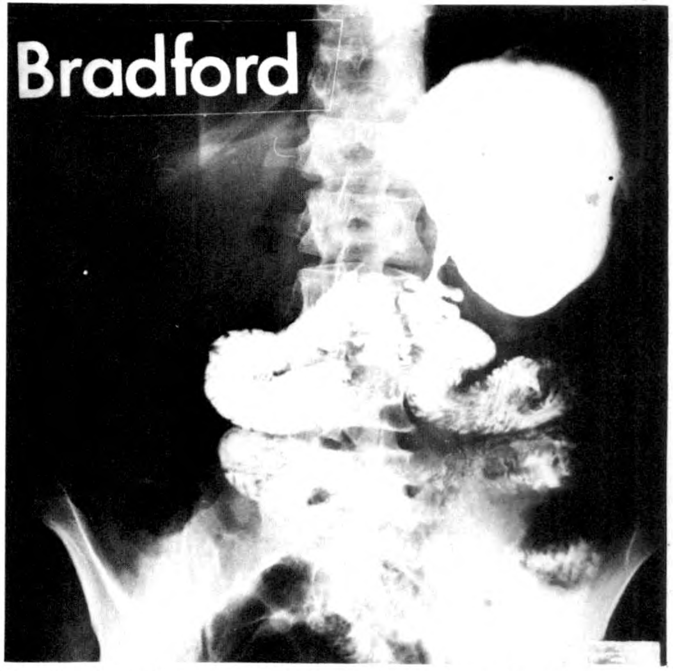


Fig. 8. The only poor result from an antiperistaltic jejunal segment. The interposed segment was too long (18 cm.). Over a 4-year period multiple ulcers and stenosis developed as shown in x-ray. After replacing this segment with 8 cm. long segment, patient did well.

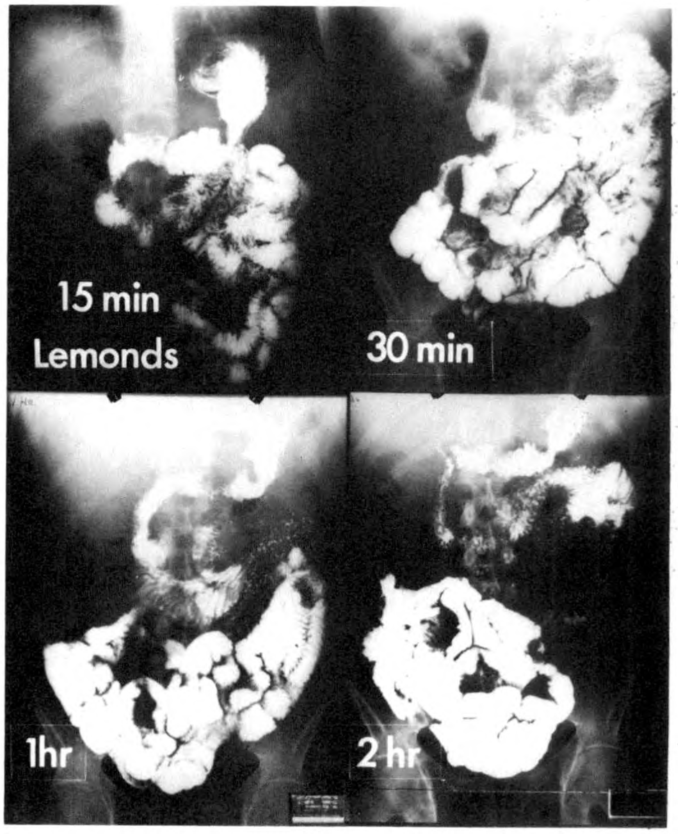


Fig. 9. X-rays of barium meal in patient with 10 cm. long antiperistaltic jejunal segment which acts as substitute pylorus to delay gastric emptying. Segment functions effectively 10 years after remedial operation.

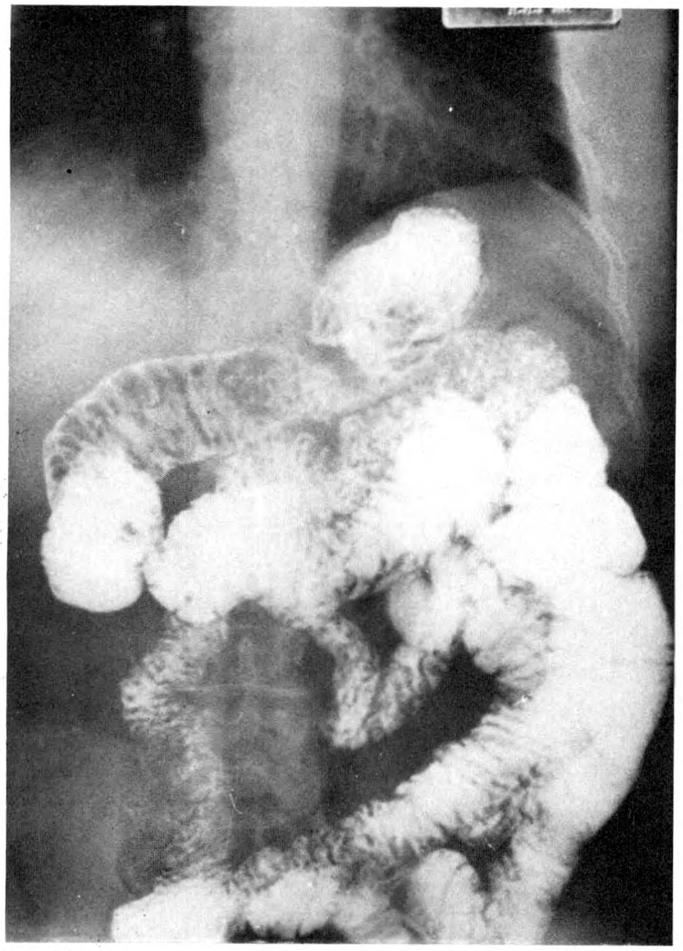


FIG. 10. Isoperistaltic jejunal segment fails to slow gastric emptying of barium meal. Dumping symptoms were not relieved.

TABLE 2. *Results in 50 Patients Shows the Superiority of using a Single 10 cm. Antiperistaltic Jejunal Segment in Patients with Intractable Dumping Syndrome.*

	Number of Patients	Satisfactory Results
Isoperistaltic Segment	10	20%
Double Limb Pouch	12	58%
Antiperistaltic Segment	28	93%

these segments may enlarge the gastric reservoir, there is no delay in gastric emptying time (Fig. 10). Ciné studies show the barium meal to speed on through the isoperistaltic segment. The pyloric valve-like mechanism of the reversed segment is lacking. Our patient who achieved a good result after reversal of a previously placed isoperistaltic jejunal segment nicely illustrates the necessity of achieving delayed gastric emptying to alleviate dumping symptoms.

The double limb jejunal pouch interposed between the gastric remnant and duodenum creates a satisfactory gastric reservoir and by anastomosing the antiperistaltic limb to the duodenum, gastric emptying time is delayed. However, after a period of time the pouch may dilate and enlarge to such a degree that stasis occurs in the pouch (Fig. 11). The patient then complains of upper abdominal discomfort. Woodward[16] and Lawrence[7] have seen this problem develop in their triple looped jejunal pouches. From our experience with the double limb pouch, we would advocate its use only in patients who suffer from the small gastric pouch syndrome after 85 to 90% high subtotal gastric resection. In patients who had gastric resections of 50 to 60%, insertion of a jejunal pouch will eventually result in dilatation of the pouch with inadequate gastric emptying.

The 10 cm. antiperistaltic single jejunal segment appeared to function satisfactorily, without serious sequelae developing, during our follow-up studies which extend to 11 years. The operation is technically simple. The jejunal segment is passed through the transverse mesocolon, rotated counterclockwise to an antiperistaltic position and interposed between the gastric remnant and duodenum. Vagotomy is performed in those patients who have not had complete gastric vagotomies. In patients who have had pyloroplasties, we have removed the antrum for fear of producing antral stasis and stimulation of acid secretion by the gastrin mechanism. Stemmer and associates,[14] however, have interposed 4 to 6 cm. antiperistaltic segments between the stomach and duodenum without antrectomy and report no gastric ulcerations.

We have had no experience in the use of pyloric reconstruction for treatment of the dumping syndrome. Regan[11] reported good results in four patients with dumping syndrome after reconstruction of the pylorus which narrowed the lumen to admit only one finger. The longest follow-up period in his patients was 17 months. Several years ago, we attempted to treat the dumping syndrome in patients who had Billroth II

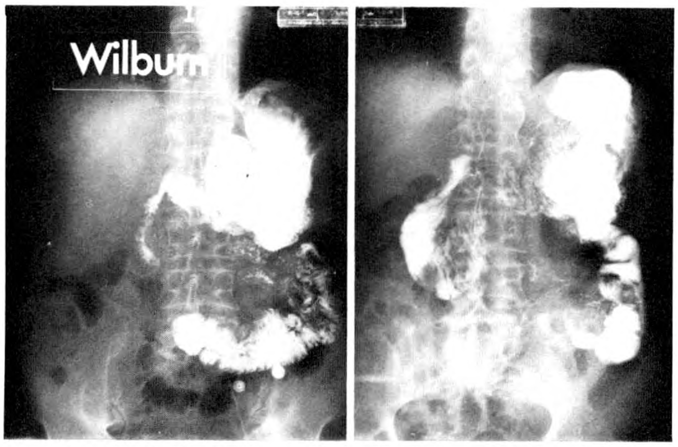


FIG. 11. Double limb jejunal pouch interposed between gastric remnant and duodenum creates a satisfactory gastric reservoir, but in a few years tends to enlarge to such a degree that stasis occurs and the pouch empties poorly.

gastrojejunostomies by converting their anastomosis to a Billroth I gastroduodenostomy. This procedure did not relieve their symptoms.

Table 2 summarizes the results in the 50 patients who underwent remedial operation for dumping syndrome by interposition of jejunum between the gastric remnant and duodenum. A single 10 cm. antiperistaltic jejunal segment gave superior results and is our operation of choice for severe, intractable early postprandial dumping syndrome.

Summary

The effectiveness of three remedial operations for management of early postprandial dumping syndrome is compared. Ten patients with isoperistaltic jejunal segments interposed between the gastric remnant and duodenum had no excellent results and good results were obtained in only two patients. In 12 patients with double iso-antiperistaltic jejunal limb pouch, excellent or good results were obtained in seven patients (58%). Unfortunately, these pouches tend to dilate and empty poorly after several years.

The best results were obtained by using a 10 cm. single antiperistaltic jejunal segment interposed between the gastric remnant and duodenum. Twenty-six of 28 patients (93%) had good to excellent results. Follow-up studies extending to 11 years demonstrate that these antiperistaltic segments continue to function effectively.

References

1. Hedenstedt, S.: Gastrectomy with Jejunal Replacement. Acta. Chir. Scand., 117:295, 1959.
2. Hedenstedt, S.: Experience with Gastric Resections with Transpositions of the Jejunum and Vagotomy. Acta. Chir. Scand., 125:518, 1963.
3. Henley, F. A.: Experiences with Jejunal Interposition for Correction of Postgastrectomy Syndromes, p. 777 in Surgery of the Stomach, 2nd ed., Harkins, H. N. and Nyhus, L. M., Boston, Mass., Little, Brown and Co., 1969.
4. Jordan, G. L., Jr., Angel, R. T. McIlhaney, J. S., Jr. and Willms, R. K.: Treatment of the Postgastrectomy Dumping Syndrome with a Reversed Jejunal Segment Interposed between the Gastric Remnant and the Jejunum. Am. J. Surg., 106:451, 1963.
5. Jordan, G. L., Jr.: Surgical Management of Postgastrectomy Problems. Arch. Surg., 102:251, 1971.
6. Krause, U.: Partial Gastrectomy with Jejunal Transposition: A Follow-up Investigation of 80 Patients Treated Operatively. Acta. Chir. Scand., 123:132, 1962.
7. Lawrence, W. J., Jr.: Personal Communication, 1973.
8. Mix, C. L.: Dumping Stomach, Following Gastrojejunostomy. Surg. Clin. N. Am., 2:617, 1922.
9. Poth, E. J.: The Dumping Syndrome and its Surgical Treatment. Am. Surg., 23:1097, 1957.
10. Poth, E. J.: Surgical Correction of Severe Dumping and Postgastrectomy Malnutrition; A Therapeutic and Diagnostic Test. Ann. Surg., 160:488, 1964.
11. Regan, J. F., Schmutzer, K. J. and Stemmer, E. A.: Procedures of Value for the Prevention and Cure of Dumping after Vagotomy and Pyloroplasty. Am. J. Surg., 124:279, 1972.
12. Sanders, G. G.: Interposed Jejunal Segments in Ulcer Surgery. J. Kentucky Med. Ass., 63:855, 1965.
13. Schlicke, C. P.: Complications of Vagotomy. Am. J. Surg., 106:206, 1963.
14. Stemmer, E. A.: Personal Communication, 1973.
15. Woodward, E. R.: The Postgastrectomy Syndromes. Springfield, Ill.: Charles C Thomas, 1963.
16. Woodward, E. R.: Personal Communication, 1973.

DISCUSSION

DR. EWARD A. STEMMER (Long Beach): As you all know, the postgastrectomy syndrome is actually a mixture of abnormalities of which the dumping syndrome is only one. Since each of the postgastrectomy syndromes differ in etiology, it is essential that the specific syndrome be actually identified if treatment is to be effective. Establishing the diagnosis of dumping syndrome is more difficult than it may seem as demonstrated by the wide variation in the incidence of this complication reported in the literature.

Some of the confusion in the diagnosis of the dumping syndrome undoubtedly results because this entity is primarily one of symptoms rather than physical findings. As a result of animal studies conducted several years ago, we concluded that the small bowel transit time, the peak plasma insulin response and the blood glucose response after a test meal were useful objective measurements in the diagnosis of dumping syndrome. In addition, we consider it essential that the patient have both vasomotor and gastrointestinal symptoms before a diagnosis is considered established. Abdominal pain is not a prominent part of the dumping syndrome and we would question such a diagnosis if the patient's primary complaint is abdominal pain. Moreover, we discovered that if the patient's primary problem is psychiatric or a desire for compensation the results of operation are likely to be poor.

While few patients with dumping syndrome require surgical correction, we agree with the authors that antiperistaltic segments can be employed with good success provided that the diagnosis of dumping syndrome is actually established.

DR. EDWARD ROY WOODWARD (Gainesville): The authors are to be congratulated on these outstanding results in a most difficult, iatrogenic clinical problem.

In 1954, Hastings and I first used a three-limb jejunal pouch as a replacement for a subtotally resected stomach with severe dumping, and as luck would have it, our very first patient had a brilliant result. He gained 65 pounds in the first year after operation. He had the amazing good judgment to move from Los Angeles to Florida so that I have been able to follow him for 19 years since that surgery. He has continued to be totally asymptomatic and has had no difficulties whatever with his artificial stomach.

We proceeded to treat a total of 12 patients cases from 1954 to 1963 and only once did we duplicate this result. We had the same experience that the authors report with the two-limb jejunal pouch; *i.e.* failure of adequate emptying, progressive dilatation of the pouch and symptoms of prolonged retention of ingested material. Nearly all of these pouches have been either removed or drastically revised and we do not believe that this procedure has a useful place in treating the early postprandial dumping syndrome.

We have used the isoperistaltic "Henley loop" interposition for patients with chronic afferent loop syndrome, and the results are very good. In those patients who also had early postprandial "dumping," many have noted some improvement in these symptoms. In most such cases, however, this is neither dramatic nor longlasting.

It is our experience that if there is a relatively large gastric remnant, a simple Billroth II to Billroth I conversion gives reasonable symptomatic improvement. This coincides with progressive significant weight gain in about 85% of the cases.

I would like to point out that the best treatment for this horrendous problem is prevention. As Dr. Dragstedt always likes to say, "the stomach is a very handy organ to take to the dinner table with you!"

Dr. Walter H. Gerwig, Jr. (Santa Barbara): I was privileged to read this manuscript and following our Presidential Address this morning, I reread it during the noon hour utilizing the criteria that Dr. Rhoads had mentioned. I assure you that this manuscript does have the quality and the high caliber that he so emphasized.

I share with Dr. Stemmer and Dr. Woodward their compliments for the study that has been carried out and reported here by Dr. Sawyers and Dr. Herrington.

It is said that, beauty is only in the eye of the beholder and therefore, I wish to mention that the isoperistaltic segment procedure, which I favor, should not be totally disregarded.

The March issue of the *American Journal of Surgery* contains information on our most recent data concerning the isoperistaltic interposed jejunal segment as a method of management of the severe, unrelenting dumping syndrome.

In this article we reported the results in 11 patients with severe dumping out of a total of 600 patients undergoing gastric surgery over a 20-year period. In these patients, an isoperistaltic jejunal segment was interposed between the stomach and the duodenum. We feel that this procedure has provided us with a valuable modality for the management of severe dumping syndrome.

Of the 11 patients, six were operated upon by me between 1962 and 1967 and hence have provided us with follow-ups of from 6 to 11 years. I wish to confine my remarks to these six patients using weight, tolerance to carbohydrate intake and the ability to take water with their meals as criteria for assessing our follow-up results.

All six patients had had their symptoms in excess of 7 years before being subjected to this method of surgical management. Five patients had good results. One of these died in the seventh postoperative year of an automobile accident. The other four are living and well today. One patient gained over 25 pounds during the first year and has maintained that weight. A second patient is 40 pounds over his ideal weight.

I was interested in Dr. Stemmer's remarks about compensation because I think that it is a factor in those patients who might be receiving some income as the result of their illness and therefore somewhat reluctant to express a feeling of excellent well-being and then be required to give up their compensation. The sixth patient received little benefit from the procedure and was followed from that time until his death in the fourth postoperative year from carcinoma of the lung. Based on these follow-ups in excess of 6 years we feel now that the isoperistaltic jejunal segment has resulted in a very good response with relief of symptoms in five of six patients.

It's interesting that in 1967 we reported seven patients with severe dumping of 400 gastric operations which is about 2%, or twice the incidence that Dr. Sawyers mentioned. In March, 1973, we report an additional 200 patients who had undergone gastric surgery, 18 of whom became severe dumpers, an incidence of 3%. I wonder if this represents an increase of the problem and/or a better recognition of the syndrome.

I might add that vagus resections are certainly needed if it has not already been provided in the isoperistaltic patient. I also would strongly suggest that it does not necessarily need resectional therapy to cause our difficulty. One of the worst problems that we were confronted with was that of a vagus resection and a pyloroplasty. Dr. Sawyers used up to 25 cm. segment but ours have all been longer than that.

Dr. Carl Schlicke (Spokane): A number of years ago when Dr. Alton Ochsner gave The Grey Turner a lecture at the International Society of Surgery he had some rather disparaging remarks to make about vagotomy and drainage procedure in the treatment of peptic ulcer.

The ultimate condemnation which he was able to invoke was that any operation which for the relief of its sequelae might require, as he put it, that most unphysiologic of all procedures, the interposition of a reverse intestinal loop, must be basically unsound.

About 10 years ago in a paper dealing with complications of vagotomy, we had reported what was for us an act of desperation, namely the interposition of such a loop between the stomach and duodenum in a woman with devastating diarrhea and 30 pounds weight loss following vagotomy and antrectomy.

This lady's problems were completely relieved to her satisfaction and ours and yet in the ensuing years we have only performed three more operations of this type.

These are just a few comments I would like to make. In the first place, it is indeed a rare patient whose problems following a gastric operation merit consideration for this type of surgical intervention. Secondly, I agree with Dr. Sawyers and Dr. Herrington, that if all else fails and one is unable to afford such a patient relief from intractable dumping, diarrhea and weight loss by any other means, that the use of a reversed jejunal segment seems to be the most satisfactory way of coping with the problem. It is far simpler than the construction of a pouch and it does effectively slow gastrointestinal transit time.

I have had no experience with the isoperistaltic loop except in individuals with severe regurgitation of bile and alkaline gastritis. It sort of seems to me like the horizontal escalators at the airport!

The third thing is that not the least of the problems is the difficulty of evaluating the results of performing this operation. Some patients seem to be improved by whatever type of revision is carried out, even as has been mentioned, the conversion of a Billroth II to a Billroth I anastomosis. Fortunately, we do have a more objective yardstick than just the patient's statement of his subjective improvement and that is the measurement of the rate of gastric emptying, the intestinal transit time and the glucose studies.

Finally, I am truly concerned that with all that has been written about this operation, of late, that it may become more widely attempted than can be really justified.

Dr. Walter Lawrence, Jr. (Richmond): I feel that Dr. Sawyers and Dr. Herrington have really made a major contribution to our thinking in the choice of a remedial operation. Such an operation is rarely indicated I believe but they have shown us the preferable procedure when it is. I thought I would use this occasion to retract something that we reported some 10 years ago regarding remedial operations for the dumping syndrome. Our experience really points up the value of long-term follow-up such as Dr. Sawyers has presented to us today.

At that time, we published a very enthusiastic report on the use of an interposed triple lumen pouch very similar to the one described by Dr. Woodward. All of the patients gained weight promptly and it was encouraging to us as the symptoms did improve. However, the defect in the report was that there was only a 2-year follow-up and on continued follow-up of these patients, our experience was very similar to that of Dr. Woodward—the pouch got bigger, and reoperation was sometimes required.

In general, I think we learned the lesson that you can speak too soon about results. I really appreciate the opportunity to be able to give you this follow-up without having to go through the embarrassment of writing a paper about it!

Dr. George Lyman Jordan, Jr. (Houston): I, too, would like to congratulate the essayists on this paper because I think that it brings up a real solution to a problem that has bothered surgeons for many years. Whereas we would like to operate upon patients and have them no longer troubled with any problems, the fact of the matter is that some patients, who are subjected to gastrectomy or vagotomy and a drainage procedure, with or without resection, will have dumping syndromes. I think it is rather amazing rather than disturbing that only 25 to 30% have these symptoms. I do fully agree, however, that most of these symptoms are controlled by medical therapy and only the occasional patient needs an operation.

As indicated by the previous discussers, as well as Dr. Sawyers presented in the paper, there has been a long search for surgical procedures to handle the patients who do have symptoms so severe they cannot be controlled and I agree with him that the basic problem is the rapid emptying of the stomach. Thus, the operation he has described today which definitely slows gastric emptying would appear to be the most rational procedure and I think the discussers of this paper as well as his own statistics support this concept. Our own experience also supports him. We have been performing this operation now for about 12 years and we agree it is rarely indicated. Our experience is not extensive. It includes 11 patients, but the results also are good.

I would just like to make one comment about technic, however, because we have used four different technics under different circumstances and this is the one (slide) we first developed in the dog and we used only a 6 cm. segment. I think this is too short and agree completely that a 10 cm. segment currently is the length of choice. It is long enough to routinely delay emptying without causing obstruction. This procedure we no longer perform although it was used successfully in the human and this is my preferential procedure. It is easier I think than the procedure that is shown in Dr. Sawyers' illustration. It accomplishes the same physiologic results. We have utilized this procedure too as have others and it, too, relieved symptoms because it prevents rapid passage of food into the jejunum. We also have used this technic in patients who have had vagotomy and pylorplasty, a vagotomy and a Billroth I. This, too, is technically simpler and accomplishes the same objective; namely, the prevention of passage of food rapidly into the jejunum.

I think, therefore, we have made considerable progress in the prevention and correction of symptoms which may follow gastric surgery. With more limited resections we no longer produce small stomachs syndrome. We can correct bile reflux when it occurs. This technic not only will correct the dumping syndrome but also will correct the hypoglycemic syndrome which occurs. Therefore, with the very low incidence of poor results following this procedure, we now should be able to rehabilitate virtually all of the patients who have difficulty following gastric surgery.

Dr. Edgar J. Poth (Galveston): The Authors have compared a simple reversed segment with the substitute gastric pouch with an antiperistaltic outlet fashioned from a long segment of jejunum. This jejunal substitution pouch should be reserved for use when more than 85% of stomach has been resected and a simple reversed segment would be inappropriate unless placed distal to the duodenum in the proximal jejunum. The reversed segment described by Dr. Jordan in his discussion uses a longer jejunal segment, having at least two arteries in the mesenteric pedicle thereby affording a better blood supply, appliqueing the major portion of the jejunal segment to the end or lesser curvature side of the residual gastric pouch to increase the gastric volume. The remainder of the jejunal segment is used to supply an appropriately long, reversed section between the enlarged gastric pouch and the duodenum. While both of these procedures are reported in a single publication (*American Surgeon*, **23**:1097–1102, 1957), the latter one (*Amer. Surg.*, **23**:1100, 1957 Fig. 2-B) is, to the best of my knowledge, the first reversal to be performed intentionally on man (1954) and was based primarily on the experimental observations made by Halsted and published by Mall (Mall, F. P.: Reversal of the Intestine, *Johns Hopkins Hospital Reports*, **1**:93, 1896).

Experience obtained from the use of this procedure for approximately 20 years indicates that the length of the reversed portion of the segment varies greatly with the size and peristaltic activity of the residual gastric remnant and should seldom exceed 5 cm. The portion of jejunum appliqued to the residual gastric pouch also serves to decrease the rate of emptying.

Chairman Merendino: This paper obviously has generated great interest. Dr. Sawyers, while you are coming up to close, would you think about answering a minor technical question. You implied there is a certain length which is right or correct and others, in discussion, have indicated that possibly success may be accomplished with a segment of lesser or greater length. My question is how is the segment measured? Depending upon how it is measured, *i.e.* whether it's stretched and how much, whether it is measured on the anti-mesenteric or the mesenteric border, etc.—we may be talking about approximately the same length, thus reconciling the ranges between 6 and 14 cm. referred to by others.

Dr. John L. Sawyers (Closing): We are certainly honored to have so many distinguished surgeons discuss our paper. Each discusser has had considerable experience in the surgical management of the dumping syndrome and has been a pioneer in this field. Their comments generally tend to support our findings that 10 cm. antiperistaltic jejunal segments are effective in relieving the severe vasomotor symptoms of postprandial dumping.

Dr. Woodward mentions success with conversion of Billroth II anastomoses to Billroth I. We tried this several years ago but were not successful in relieving many patients of their symptoms.

Dr. Gerwig points out his success with isoperistaltic jejunal segments. Henley has also had satisfactory results with this technic. Their results may be different from ours because the jejunal segment is longer. We have avoided long isoperistaltic segments for fear of stasis and kinking in the jejunal loops.

Dr. Merendino asked how we measure the length of our interposed jejunal segment. We isolate a length of jejunum about 40 cm. distal to Treitz's ligament. With the bowel held on a slight stretch between Babcock clamps, we measure a 10 cm. length placing the tape measure or ruler midway between the mesenteric and antimesenteric border of the bowel. The divided jejunal segment is brought up behind the transverse colon, reversed and sutured end-to-end between the gastric remnant and duodenum. As Dr. Jordan mentioned, the end may be sutured into the side of the duodenum rather than end-to-end if this is technically easier.

In conclusion, I would stress, as have the discussers, that very few patients need remedial operation. Most patients with dumping syndrome can be satisfactorily controlled by manipulation of their diet. However, there are a few patients who are severely incapacitated with marked weight loss because they are afraid to eat. They cannot carry on their livelihood. These patients are greatly benefited by remedial operation.

Significance and Treatment of Occult Obstructive Uropathy Complicating Crohn's Disease

GEORGE E. BLOCK, M.D., M.S. (Surg), F.A.C.S.,* WARREN E. ENKER, M.D.,*
JOSEPH B. KIRSNER, M.D., PH.D.**

From the Departments of Surgery and Medicine, The University of Chicago Hospitals and Clinics, Chicago, Illinois 60637

IN 1970, we reported six cases of occult, right-sided ureteral obstruction which occurred in patients suffering from fistulous complications of Crohn's disease.[6] A ureteral abnormality coincident to Crohn's disease was first noted by Hyams, Weinberg and Alley in 1943 and has been sporadically reported during the ensuing 30 years.[2,9,10,12,16] Despite the association of these two entities, their clinical significance and their appropriate treatment have not been elucidated.

We have encountered the entity of an occult, right-sided obstructive uropathy complicating Crohn's disease of the ileum or ascending colon in 27 patients. It is our thesis that the obstructive uropathy is caused by a cicatrix consequent to a right-sided septic retroperitonitis attributable to advanced Crohn's disease complicated by sinus, fistula, or abscess.

The demonstration of ureteral obstruction complicating Crohn's disease is an indication for operation for relief of both the advanced ileocolitis and the urinary tract obstruction. Appropriate resection of the involved bowel supplemented by ureterolysis has proved to be an effective remedy for the relief of the intestinal and urinary tract disease in all of our patients.

Material

From 1967 through 1972, 27 patients exhibiting both Crohn's disease and right ureteral obstruction were treated by resection and ureterolysis. During this period, we performed resections in 106 patients suffering from Crohn's ileocolitis primarily involving the terminal small bowel and ascending colon. This does not represent a true incidence of this complication as the majority of our patients were referred from other services or institutions and usually were patients with the spectrum of advanced and complicated Crohn's disease.

Seventeen patients were male and ten were female. There were 24 Caucasians and three Negroes. The youngest patient was 17 years of age and the oldest was 59. The average age at the time of operation was 25.5 years. At the time of operation for obstructive uropathy, the average duration of known granulomatous disease was 3.9 years. Two patients were unaware of the presence of Crohn's disease until they suffered urinary symptoms. Three of the 27 patients had previous operations for regional enteritis. None of our patients had prior attempts to alleviate the urinary tract obstruction.

Symptoms and Physical Findings

The 27 patients comprising this series all suffered from Crohn's disease of varying severity and localization. While some patients had granulomatous involvement of the entire colon as well as the terminal small bowel, all had one feature of the disease in common: the site of greatest severity of the disease was in the ileocecal region. The symptoms varied greatly from mild cramping and diarrhea to severe cachexia and inanition. Certain symptom complexes, as well as physical, laboratory, and roentgenographic findings were noteworthy as they defined clinically the presence of retroperitonitis and ureteral obstruction.

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25–27, 1973.

* Department of Surgery.

** Department of Medicine.

Twenty-one of the 27 patients (78%) exhibited a right lower quadrant mass by abdominal, rectal, or vaginal examination. Seven patients complained primarily of right flank or CVA pain or tenderness. The right kidney of one individual was enlarged, palpable and tender. Five patients had histories of lower urinary tract symptoms such as frequency, dysuria, or suprapubic and groin pain.

Fifteen of the 27 patients had grossly abnormal urinary sediment on routine examination. Of perhaps greater significance is the fact that 12 patients had normal urinalyses.

Twenty-one patients had sterile urine cultures. The six patients with contaminated urine all demonstrated *Escherichia coli* in quantities greater than 100 thousand colonies per milliliter. One of these patients also harbored *Aerobacter aerogenes* and another was infected by *Proteus mirabilis* in quantities greater than 100 thousand per milliliter. Two patients with positive cultures suffered an entero-vesical fistula in addition to hydroureter and hydronephrosis.

Roentgenographic Findings

Gastrointestinal

Gastrointestinal contrast roentgenograms in all patients were diagnostic of Crohn's disease. The barium enema X-ray with views of the terminal ileum was particularly rewarding. In addition to delineating the extent of ileal disease, the roentgenographic findings included enterocolic and entero-vesical fistula, psoas abscess formation, entero-cutaneous fistula, etc.[7] Of particular importance in retrospect were the two most common findings: high grade partial ileal obstruction from Crohn's disease with or without sinus tracts from the ileocecal region to abscess cavities in the retroperitoneum. This demonstration of the supposed pathogenesis of the syndrome was observed roentgenographically in 17 of the 27 patients (Fig. 1).

Cystopyelography

The most rewarding single preoperative diagnostic examination was the excretory pyelogram (IVP). Occasionally, this examination was supplemented by either cystogram or retrograde pyelography. One patient underwent emergency laparotomy and a preoperative IVP was necessarily omitted. In all other patients, ureteral obstruction with varying degrees of hydroureter and hydronephrosis were demonstrated prior to operation. Eighteen of the 26 patients undergoing preoperative excretory urograms were found to harbor occult, right-sided hydronephrosis in addition to the hydroureter. One entero-vesical fistula also was demonstrated by this means.

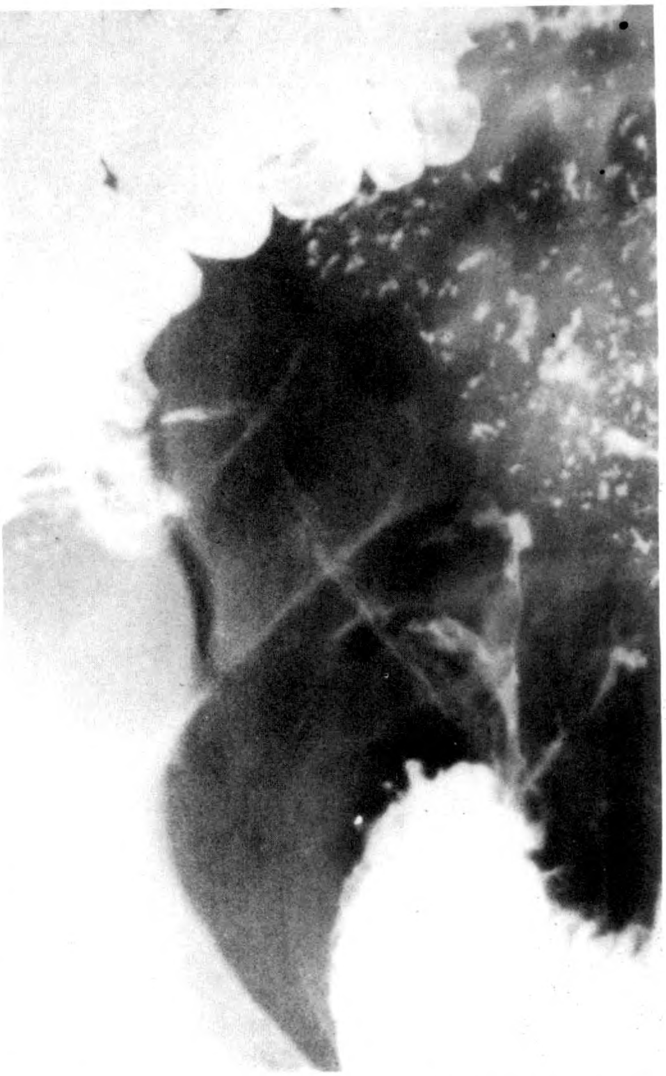
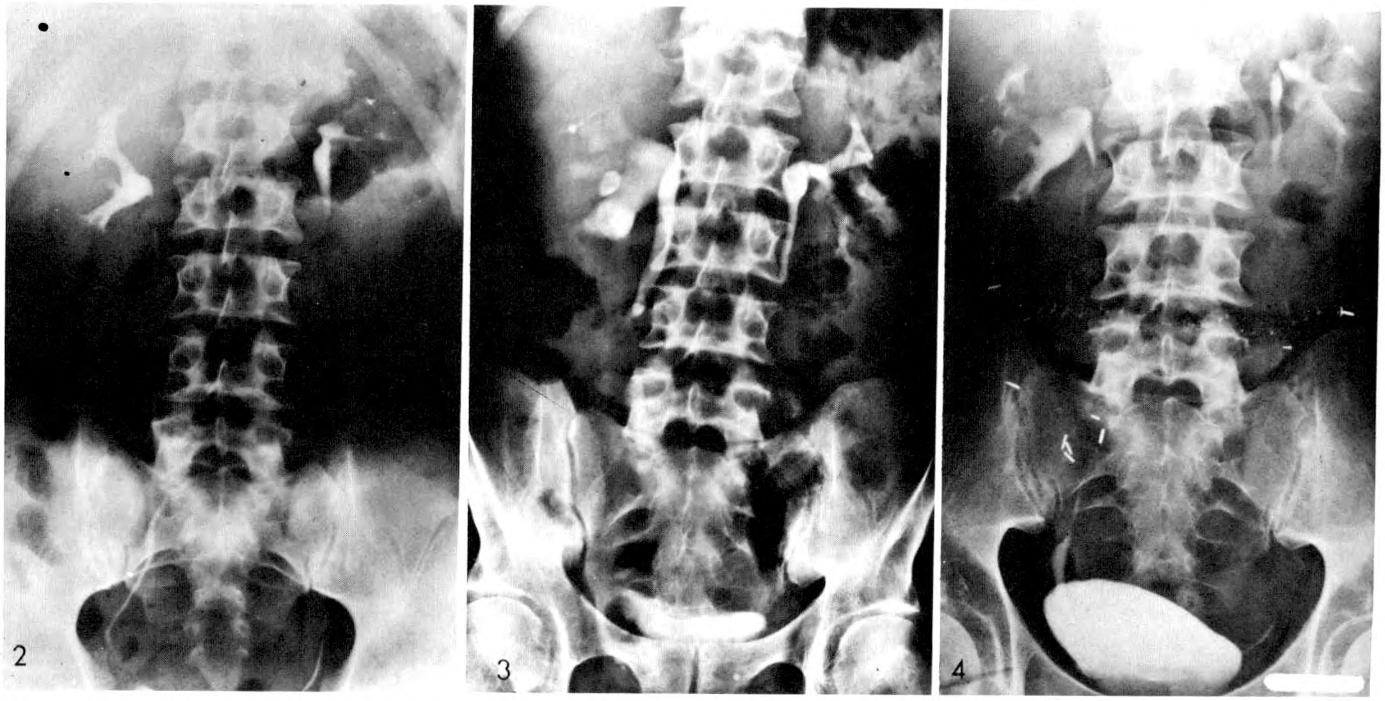


FIG. 1. Barium contrast roentgenogram of the ileo-cecal region demonstrating sinus tracts into the retroperitoneum. The origin of the sinus is proximal to a partial bowel obstruction. The proximal bowel is dilated. This patient suffered retroperitonitis with an anterior retroperitoneal abscess.

In three patients, serial pyelograms prior to operation demonstrated the *sudden* development of right hydroureter and hydronephrosis coincident to clinical worsening of the intestinal disease.

In one patient in whom a double collecting system was present on the right side, both ureters were obstructed.

Pre-voiding views of the bladder observed at the time of pyelography uniformly revealed a defect attributable to Crohn's disease. In those patients with severe ileal disease, the right posterior dome of the bladder was persistently indented. This deformity corresponded to the outline of the inflamed and thickened small bowel. It did not represent either primary or secondary vesicle disease, as cystoscopy did not dis-



FIGS. 2, 3 and 4. Representative views of sequential excretory urograms. The first pyelogram in 1969 (Fig. 2) shows normal renal architecture. Figure 3 is a pyelogram taken in 1972 during an episode of severe exacerbation of the ileitis. There is obvious hydroureter and hydronephrosis. Following intestinal resection and ureterolysis (Fig. 4), the pyelogram has returned to normal.

close mucosal changes and the outline of the bladder returned to normal after resection of the offending segment of bowel. This finding has not been previously emphasized, but has proved to be a reliable index of advanced Crohn's disease for us. Despite scrupulous investigation, none of our patients was found to have renal or ureteral calculous disease to account for their dilated ureter (Fig. 6).

Operative Findings

At operation, all patients were found to harbor active Crohn's disease and the individual findings varied according to the extent of visceral disease, degree of obstruction, site of fistulae, etc. Each of the patients had certain features of Crohn's disease in common. These were severe Crohn's disease in the right lower quadrant penetrating through the visceral peritoneum and the posterior parietal peritoneum with resultant retroperitonitis. The area of penetration and retroperitonitis corresponded to the previously palpated mass in the 21 patients so recorded. Twenty-four (89%) of the patients exhibited a fistula or sinus tract from the involved ileocecum to the retroperitoneum. Eleven patients (41%) had frank abscesses of the anterior retroperitoneal compartment. In one patient, this abscess involved all compartments of both the anterior and posterior retroperitoneal spaces.

In all patients with hydroureter, the right ureter was found to be encased in the cicatrix of retroperitoneal fibrosis. Two patients had ureteral obstruction above the level of the pelvic brim: one at the site of recurrent bowel disease and another in the retroperitoneum from residual fibrosis 3 years after bowel resection without ureterolysis.

The degree and extent of fibrosis varied greatly from patient to patient. In a few patients, the fibrosis was moderate and was easily dissected from the ureter. In the majority, the fibrosis was dense, thick and intimately encased the ureter from the pelvic brim to the trigone of the bladder. In these patients, dissection to completely free the ureter from the cicatrix was excruciatingly difficult. The ureteral obstruction occasionally produced huge proximal dilatation of such a degree that the ureter approximated the diameter of the small bowel. The obstructed distal segment of ureter gradually tapered into a dense cicatrix. The ureter at this point frequently was compressed to only a few millimeters in diameter. The involved ureter appeared ectatic and, in addition to dilatation and secondary inflammation, the walls of the ureter were thickened. No ureteral biopsies were taken.

During the early portion of the series, biopsy specimens were obtained from the retroperitoneal cicatrix. These were reported as showing nonspecific inflammation with stellate cell formation, collagen deposition, fibrosis and diffuse edema.[6]

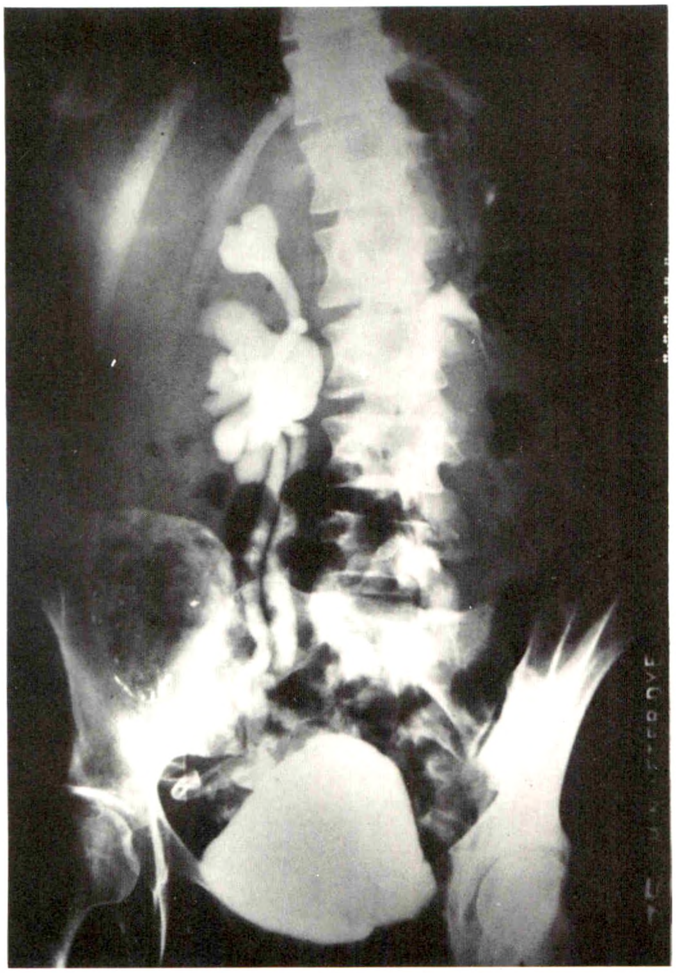


FIG. 5. Hydroureter and hydronephrosis in a patient with a right-sided double collecting system. After ureterolysis, the hydroureter and hydronephrosis resolved.

Operative Procedures

A variety of operative procedures were performed upon the patients in this series. Although varied in exact nature, all operations conformed to our basic thesis: resection of the area of bowel harboring the mechanical complication, complete ureterolysis of the involved ureter, and drainage of retroperitoneal abscesses when encountered. No intestinal bypass procedures were employed for treatment of the Crohn's disease.

One patient underwent ureterolysis only, as the Crohn's disease was resected 3 years prior to diagnosis of ureteric obstruction. Two patients underwent total colectomy, and the remaining 24 patients underwent appropriate small and large bowel resections. Fecal continuity was reestablished primarily in 23 of these patients, but one patient had a temporary ileostomy and mucous fistula. An ileo-ascending anastomosis was constructed in six patients, ileotransverse in 16, and an ileosigmoid anastomosis in one patient.

Our technic of ureterolysis is to circumferentially free the ureter from its encasing cicatrix and to resect the anterior portion of the fibrotic sheath. Following ureterolysis the freed ureter lies in a wide bed of extraperitoneal connective tissue. No attempt is made to transpose the affected ureter nor to wrap it in omentum.

Morbidity and Mortality

There were no operative nor postoperative deaths in this series of patients. There were no complications either directly or indirectly related to the ureterolysis. There was no postoperative ureteral stricture, persistent obstruction, urinary extravasation, etc.

There were seven major and two minor complications. All complications were related to the intestinal component of the disease or its concomitant sepsis. All major complications were successfully treated. These included one instance each of partial intestinal obstruction, stress ulceration, and subphrenic abscess, and four instances of inadequately drained retroperitoneal abscess. Despite the use of delayed primary closure, two patients developed wound abscesses subsequent to premature closure.

Results

The period of follow-up observation was from 2 months to 5½ years. The one individual who was followed for only 2 months died during the third postoperative month from amyloidosis complicating longstanding Crohn's disease. For all the other patients the shortest follow-up period was 6 months and the average was 26 months. Twenty-four patients have been followed for more than 1 year.

The postoperative pyelograms in all patients have

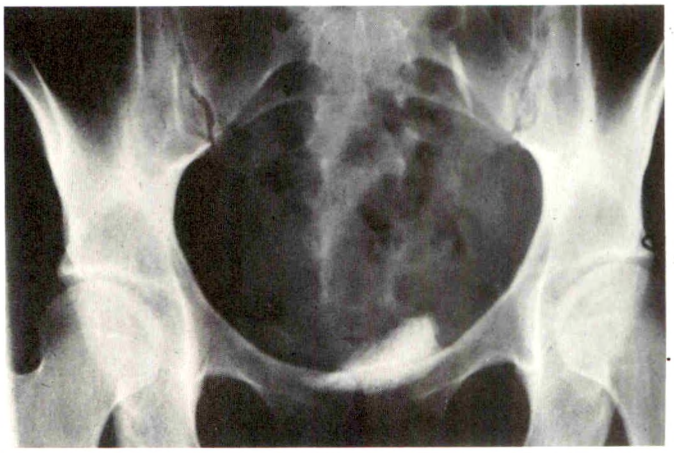


FIG. 6. Bladder deformity demonstrated by excretory pyelography. The right superior dome of the bladder is indented and deformed by the adjacent inflamed small bowel.

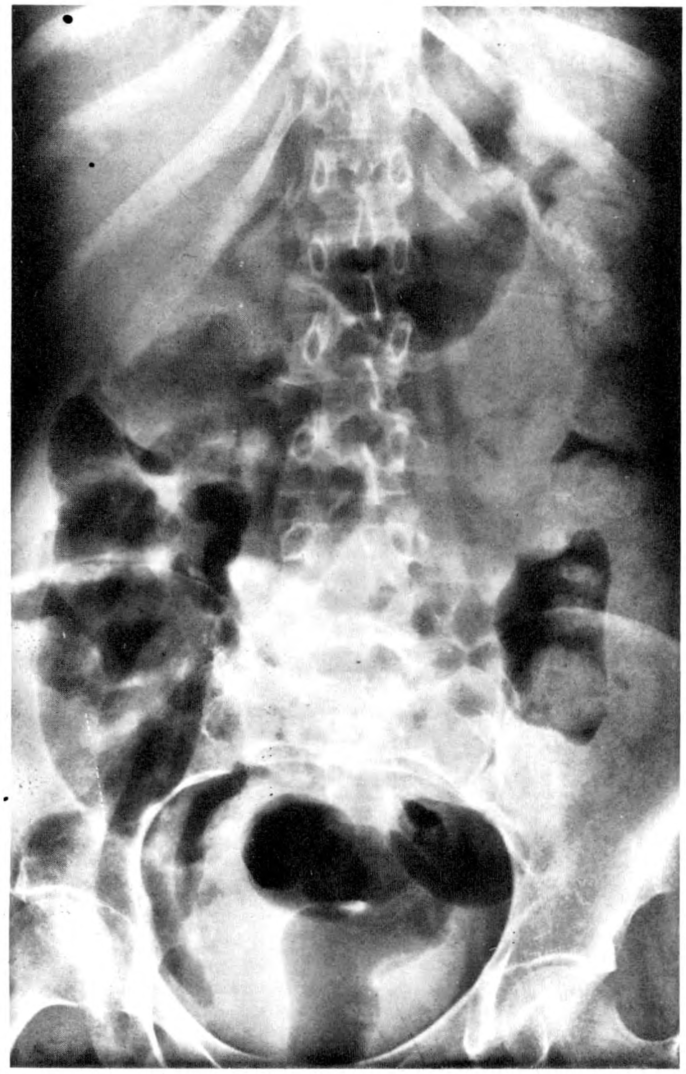


FIG. 7. Abdominal roentgenogram of patient with Crohn's disease, right ureteral obstruction and massive retroperitoneal infection. The anterior and posterior retroperitoneal space are occupied by abscesses which have also involved the subcutaneous areas of the thigh, buttocks and groin.

reverted to normal with the exception of two patients who still have minimal caliectasis without persistent ureteral dilatation. Urinary infection has resolved in all patients.

Except in those patients with vesicle fistulae, urinary bladder drainage was discontinued within 48 hours of operation. Following ureterolysis, the obstructive urinary tract infections were readily overcome by appropriate antibiotic therapy. Complete resolution of the previously documented hydroureter and hydronephrosis was evident on urography as early as 7 days following operation. Follow-up urography performed up to 42 months after operation revealed complete resolution of the obstructive uropathy in all patients.

Although it is not our purpose here to detail the postoperative course of ileocolitis, all living patients were evaluated as to the reappearance of active Crohn's disease. Twenty-two patients are free of disease while four have had recurrence of the gastrointestinal manifestations of the disease.

Bacteriology

The offending organisms contributing to the septic retroperitonitis were cultured from the retroperitoneal abscesses, fistual tracts and urine. As expected, these infections were multimicrobial and reflected the enteric origin of the pathogens. The average patient harbored two or more organisms and from one patient six pathogens were cultured. The bacteria identified in order of frequency included: *Escherichia coli*, Enterococci, *Aerobacter aerogenes*, *Pseudomonas aeruginosa*, *Streptococcus faecalis*, non-hemolytic streptococci, and Klebsiella species.

The organisms varied in their antibiotic sensitivity, but most showed convenient sensitivity to common antibiotics. Chloramphenicol, Ampicillin, cephalosporin, Gentamicin and Kanamycin were commonly indicated by *in vitro* sensitivities. In most instances, the results of cultures and sensitivities were not known at the time of diagnosis, and empiric antibiotic therapy was initiated utilizing agents known to be useful in combating both aerobic and anaerobic infections. In most cases a combination of chloramphenicol with a penicillin or cephalosporin was employed. When bacteriologic *in vitro* sensitivities became available, the antibiotic agents were modified depending upon the clinical course of the patient.

In two patients, active retroperitoneal suppuration was not found and despite proven contamination from enteric organisms, antibiotic agents were not employed. These patients made an uneventful recovery. In the overwhelming majority of patients, however, appropriate antibiotic therapy was employed to supplement resection and adequate drainage.

Discussion

The necessity for resection in Crohn's disease complicated by the septic processes of abscess, sinus or fistula is well recognized. Although bypass of the involved small bowel still enjoys some popularity, the capacity for the bypassed segment to be the site of continuing or further complications is also widely appreciated.[5] Similarly, the advisability of decompression of an obstructed ureter is well known. The long-term deleterious effects of obstruction on renal function, particularly when complicated by hemolytic *E. coli* infection, has been adequately detailed by Kass, Freid and others.[4,20]

In 1961, Altemeier and Alexander,[1] in a classic presentation concerning retroperitoneal abscesses, classified and described the retroperitoneal spaces and stated that a majority of retroperitoneal infections were secondary to primary diseases of the contiguous abdominal organs of the gastrointestinal tract. These authors reported clinical findings similar to those present in our patients with infections of the anterior retroperitoneal space, *i.e.*, right lower quadrant mass, CVA tenderness, and an unremarkable urine examination in one-third of the cases. Two of their patients suffered anterior retroperitoneal space infections due to *regional ileitis* and one due to *radiation ileitis*.

Our identification of the syndrome of obstructive uropathy complicating Crohn's disease, and our advocated treatment are, then, a synthesis of three established surgical principles: the recognition of an anterior retroperitoneal space infection, resection of the segment of bowel initiating the complication, and the relief of the mechanical obstructive uropathy.

Pathogenesis

The pathogenesis of this lesion becomes obvious when one relates the clinical course of Crohn's disease to the operative findings and the gross and microscopic pathology.

Crohn's disease of the ileum and proximal ascending colon is notorious for the complications of perforation or penetration (sinus or fistula formation). Crohn's disease of the descending colon (granulomatous colitis) infrequently is the site of origin of fistula formation and free perforation is a clinical rarity.[15] Hence, involvement of the right ureter is much more likely to occur than on the left side where the ureter is completely retrocolic throughout its pelvic course. However, two instances of left-sided ureteral stenosis complicating Crohn's disease have been documented by others.[8,10,18]

The characteristic cleft or fissure which microscopically characterizes Crohn's disease appears to be the site of serosal penetration.[17] These penetrations, in our experience, are predominantly immediately proximal to an area of luminal stenosis or obstruction. The terminal ileum and cecum are either partially retroperitoneal or in immediate juxtaposition to the posterior, lateral parietal peritoneum. Progression of the inflammatory disease through the serosa of the bowel can then easily involve the anterior retroperitoneal space in a localized phlegmon or abscess via a gross or microscopic communication. The inflammatory reaction in this region results in a retroperitoneal cicatrix that is particularly fibrous. The entrapment and obstruction of the underlying right ureter at or below the pelvic brim completes the lesion. Similar observations have been made in some cases of bilateral "idiopathic retroperitoneal fibrosis." A number of patients diagnosed as having "idiopathic" retroperitoneal fibrosis had events in their history capable of producing a retroperitoneal insult leading to fibrosis: sigmoid diverticulitis, inflammatory processes of the lower extremity, cholecystitis, etc.[1,19]

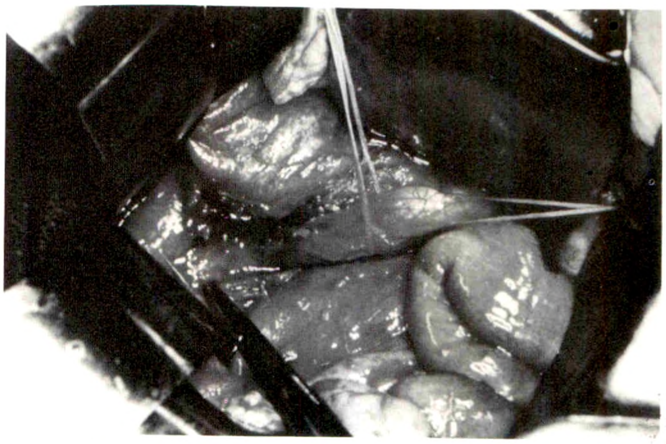


Fig. 8. Photograph taken during operation of a dilated right ureter. The ureter is isolated between umbilical tapes and disappears into the cicatrix of retroperitonitis.

Our theory of pathogenesis is attractive, easy to demonstrate and, in the end stage, can be proven by demonstration of the sinus tract to the retroperitoneum, retropertonitis, and ureteral obstruction.

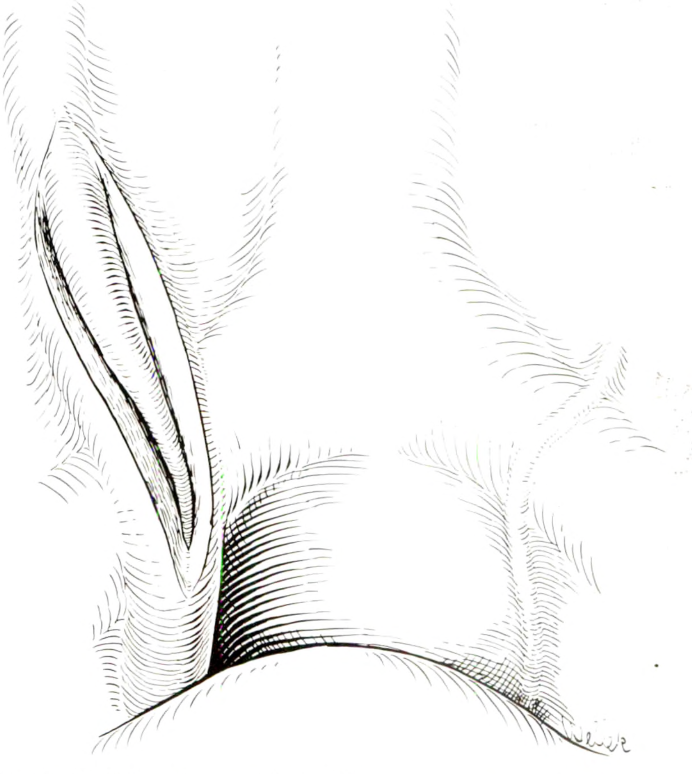
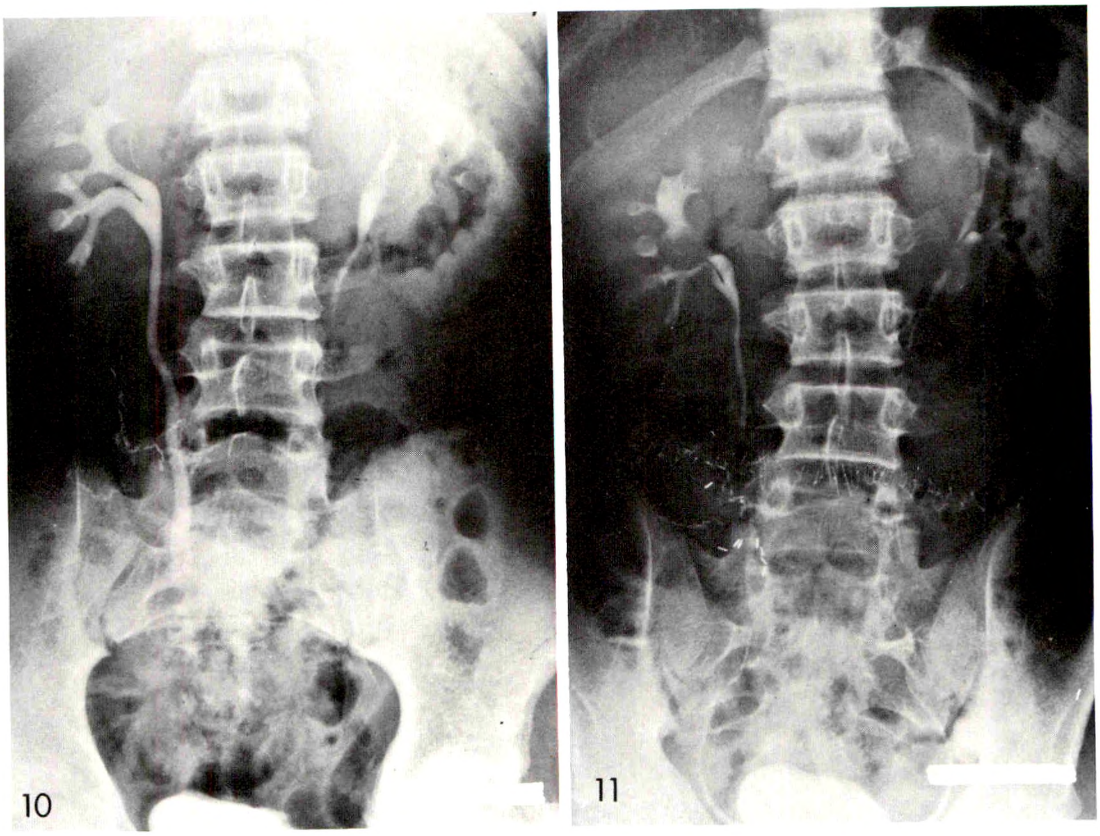


Fig. 9. Technic of ureterolysis. The ureter is circumferentially freed from the encasing cicatrix, and the anterior portion of the fibrotic sheath is resected.



Figs. 10 and 11. Excretory pyelogram (Fig. 10) of patient J. M. 3 years after intestinal resection for Crohn's disease. Hydroureter is present. Following ureterolysis (Fig. 11), the hydroureter has resolved. There was no residual Crohn's disease found at the time of ureterolysis.

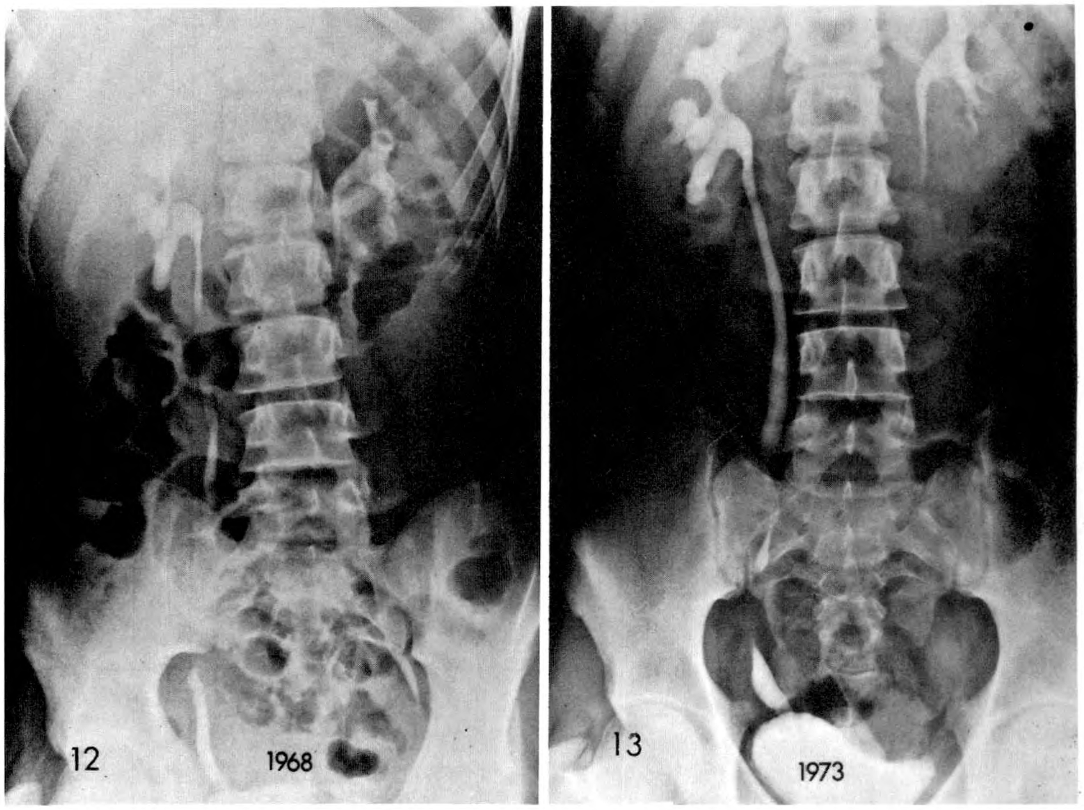
Treatment

Our advocacy of ureterolysis as a necessary supplement to intestinal resection for relief of obstructive uropathy relies upon three categories of proof: our uniform success following ureterolysis; a review of others' failures to achieve renal decompression when ureterolysis was not employed; and a presentation of the clinical course of three patients known to us in whom obstructive uropathy remained despite medical management, intestinal bypass, or resection alone. One of these patients was eventually relieved by ureterolysis.

In 27 patients the septic complications of Crohn's disease, as well as the right-sided ureteral obstruction have been uniformly relieved by resection and ureterolysis. This fact, in our opinion, is the most persuasive proof of the correctness of our position. That this result was achieved without operative mortality or urinary complication further reinforces our thesis. The absence of renal calculi in our group of patients and their maintenance of a normal collecting system up to 5½ years after operation is additional argument in favor of the necessity of ureterolysis. Monge[14] and Cerny[3] have both reported success in supplementing bowel resection with ureterolysis.

A review of the results of others in their management of ureteral obstruction with Crohn's disease lends further support to our advocated treatment. From 1943 to 1970, 22 cases of insidious right-sided periureteric fibrosis developing as a consequence of regional enteritis have been reported by others.[6] Prior to 1970, the operative treatment for the ureteral complication has primarily centered around control of the intestinal disease alone. The failure to supplement intestinal resection with ureterolysis has resulted in a continuing morbidity with a concomitant needless loss of renal function.

Hyams *et al.*, considered the origin of periureteric fibrosis to be the transport of intestinal-mesenteric inflammation to the retroperitoneum via communicating lymphatics.[12] Since their report, the spectrum of this complication has been reported to vary from minimal periureteric fibrosis with associated ureteral dilatation, to stenosis and constriction of the distal right ureter with proximal hydronephrosis. Ureterolysis for the relief of this syndrome was originally shunned because of the early unsuccessful experience encountered in ureteral decompression. Harlin and Hamm[11] warned that "intervention in the form of some surgical procedure on the urinary system is usually unnecessary and may lead to further complications." This warning was seemingly well-heeded, and the *laissez faire* attitude has resulted in a high degree of unnecessary morbidity. The failure to perform appropriate



FIGS. 12 and 13. Pyelogram of patient P.G. (Fig. 12) in 1968 demonstrating moderate occult hydroureter. There is worsening of the hydroureter and hydronephrosis in 1973 (Fig. 13). During this interval the patient was treated medically without operation.

ureteral decompression has been directly responsible for the loss of the right kidney in two patients.[11]

An objective assessment of the treatment afforded by Present, Rabinowitz and Banks[16] is not possible, as they did not record the nature of the operative treatment provided to each of the ten patients reported. Of the 12 other cases reported prior to 1969, the average patient was subjected to over two operations with one-third of the patients requiring three operations or more. Only one patient was treated by ureterolysis.[18] In this patient, as in our series, complete urinary decompression was achieved.

Of the 21 cases reported prior to 1970 which were not treated by ureterolysis, ureteral obstruction was eventually relieved in only 11. Two of the failures required nephrectomy.[11] Despite the fact that ureteral decompression was achieved in 50 per cent of patients without ureterolysis, it was achieved at the cost of at least two operative procedures per patient. It is noteworthy that of the six cases reported prior to 1969 in which there was resolution of ureteric obstruction without ureterolysis, bowel resection was employed for four patients. We may postulate that if the ureteral obstruction was above the pelvic brim, the surgeon may perforce perform an incidental ureterolysis while mobilizing the ileo-ascending colon in order to identify and spare the right ureter.

That ureterolysis is both an effective and safe procedure for definitive ureteral decompression is corroborated by the operative experience in periureteric fibrosis unrelated to Crohn's disease. This has been reported previously by Vest and Barelare[19] and Kerr, Suby and Vickery.[13]

The sequence of events occurring in two of our patients is further evidence that ureterolysis is a necessary supplement to bowel resection in order to relieve the obstructive component of this syndrome. Medical management, intestinal bypass, and intestinal resection without ureterolysis have all failed to achieve urinary decompression as witnessed by the following case studies.

Case Reports

Case 1. J. M. (969513), a 14-year-old male underwent resection of the terminal ileum and cecum for Crohn's disease complicated by right lower quadrant and retroperitoneal sinus and abscess. A primary anastomosis was accomplished and the patient made an uneventful recovery. Three years after operation the patient complained of right CVA pain. Investigation revealed extraluminal obstruction of the right ureter with hydroureter and mild hydronephrosis. At reoperation, no residual Crohn's disease was found, but the right ureter was obstructed by periureteric fibrosis. Ureterolysis resulted in prompt relief of symptoms and the pyelogram reverted to normal in less than 1 month and has remained normal for over 2 years (Figs. 10 & 11).

Case 2. P. G. (978363), a 19-year-old man was admitted to the gastroenterology service of the University of Chicago in 1968 with weight loss, inanition, and recurrent urinary tract infections. A diagnosis of Crohn's disease was confirmed and the patient was treated by an effective medical regimen. Excretory urography at the time of hospitalization demonstrated right-sided hydroureter and hydronephrosis with obstruction at the level of the pelvic brim. Operation was not advised by the primary physicians. The patient's condition regarding the intestinal disease improved, and under strict medical therapy the patient gained 50 pounds. Despite occasional episodes of partial intestinal obstruction the patient has managed reasonably well over the past 5 years. Intravenous pyelography performed in April of 1973 to evaluate the evolution of the urinary obstruction revealed persistent marked ureteral obstruction with worsening of the hydronephrosis since 1968. There have been no urinary symptoms (Figs. 12 & 13).

Conclusions

A specific and identifiable clinical entity of advanced and complicated Crohn's disease is presented. This entity consists of Crohn's disease involving at least the terminal ileum and/or ascending colon which has progressed to involve the retroperitoneum by a microscopic or gross sinus, fistula or abscess. This retroperitonitis results in a cicatricial periureteric fibrosis that, in turn, causes ureteral obstruction. This clinical entity has been observed in 27 of our patients. The urinary obstruction may be encountered in patients known to have Crohn's disease, may occur as on indication of worsening of the enteritis, or may be the first indication of previously undiagnosed Crohn's disease. Appropriate bowel resection supplemented by ureterolysis has resulted in the relief of the ureteral obstruction in all of our patients.

On the basis of our experience and observations we conclude that:

1) Routine and periodic excretory pyelograms are an essential part of the evaluation of the patient with Crohn's disease.

2) Obstructive uropathy complicating Crohn's disease is an indication for operation both for the bowel disease *per se* and for the relief of the ureteral obstruction. Obstructive uropathy indicates the presence of a classic complication of Crohn's disease: sinus, fistula or abscess.

3) Appropriate bowel resection supplemented by ureterolysis is the recommended treatment for this syndrome.

4) Ureterolysis has not resulted in any urinary tract complications nor injury to other retroperitoneal structures.

Acknowledgments

The authors wish to acknowledge and thank Commander Patrick M. McGuigan, Jr., M.C., U.S.N., Great Lakes Naval Hospital, for his contribution concerning one patient described in this report.

References

1. Altemeier, W. A. and Alexander, J. W.: Retroperitoneal Abscess. Arch. Surg., **83**:512, 1961.
2. Case Records of the Massachusetts General Hospital (Case 14-1965). N. Engl. J. Med., **272**:585, 1965.
3. Cerny, J. C.: Discussion in Enker, W. E. and Block, G. E.: Occult Obstructive Uropathy Complicating Crohn's Disease. Arch. Surg., **101**:319, 1970.
4. DePauw, A. P., Fill, W. B. and Fried, F. A.: Etiology of Pyelonephritis: Renal Lysosome Disruption by Hemolytic *Escherichia Coli.* Invest.Urol., **9**:230, 1971.
5. Enker, W. E. and Block, G. E.: The Operative Treatment of Crohn's Disease Complicated by Fistulae: A Personal Consecutive Series. Arch. Surg., **98**:493, 1969.
6. Enker, W. E. and Block, G. E.: Occult Obstructive Uropathy Complicating Crohn's Disease. Arch. Surg., **101**:319, 1970.
7. Enker, W. E. and Block, G. E.: Preoperative and Intraoperative Evaluation of Patients with Crohn's Disease and Fistulae. Surg. Clin. N. Am., **50**:123, 1970.
8. Farman, J.: Crohn's Disease with Ureteric Complications. Abstract in Proceedings of the Radiologic Society of North America, October 1971, Radiology (submitted for publication).
9. Ginzburg, L. and Oppenheimer, G. D.: Urologic Complications of Regional Enteritis. J. Urol., **59**:948, 1948.
10. Goldman, H. J. and Glickman, S. I.: Ureteral Obstruction in Regional Enteritis. J. Urol., **88**:616, 1962.
11. Harlin, H. C. and Hamm, F. C.: Urologic Disease Resulting from Non-Specific Inflammatory Conditions of the Bowel. J. Urol., **68**:383, 1952.
12. Hyams, J. A., Weinberg, S. R. and Alley, J. L.: Chronic Ileitis with Concomitant Ureteritis: Case Report. Am. J. Surg., **61**:117, 1943.
13. Kerr, W. S., Suby, H. I., Vickery, A., *et al.*: Idiopathic Retroperitoneal Fibrosis: A Clinical Experience with Fifteen Cases. J. Urol., **99**:575, 1968.
14. Monge, J. J.: Discussion in Enker, W. E. and Block, G. E.: Occult Obstructive Uropathy Complicating Crohn's Disease. Arch. Surg., **101**:319, 1970.
15. Pollock, A. V.: Crohn's Disease. Brit. J. Surg., **46**:193, 1958.
16. Present, D. H., Rabinowitz, J. G. and Banks, P. A., *et al.*: Obstructive Hydronephrosis: A Frequent but Seldom Recognized Complication of Granulomatous Disease of the Bowel. N. Engl. J. Med., **280**:528, 1969.
17. Rappaport, H., Burgoyne, F. H. and Smetana, H. F.: The Pathology of Regional Enteritis. Milit. Surg., **109**:463, 1951.
18. Schofield, P. F., Staff, W. G. and Moore, T.: Ureteral Involvement in Regional Enteritis (Crohn's Disease). J. Urol., **99**:412, 1968.
19. Vest, S. A. and Barelare, B., Jr.: Periureteritis Plastica: A Report of Four Cases. J. Urol., **38**:50, 1953.
20. Zinner, S. H. and Kass, E. H.: Long-Term Follow-Up of Bacteriuria of Pregnancy. N. Engl. J. Med., **285**:820, 1971.

DISCUSSION

DR. ALEXANDER J. WALT (Detroit): As a new member, I felt flattered when invited by my old sparring partner, George Block, to read his manuscript and to discuss his paper. My sense of pleasure was rapidly dulled, however, when I discovered that the penalty I would have to pay for this distinction would be public exposure of my ignorance! In a reasonable experience with Crohn's disease, I have personally seen only on patient with the full blown picture described by Dr. Block and in this patient, as he described, the ureter was involved in a retroperitoneal abscess with perforation of the bowel.

I could find no other examples of the entity in our own files. Dr. William Carpenter of our department kindly offered to review his own personal experience of over 100 cases which he has followed for about 15 to 20 years and he found no such case in his material, nor did he have any patient subsequently return to him for any urinary problem. In contrast, Dr. Block has given us a very clear and often dramatically documented account of his experience in which no fewer than 26% of the patients operated upon by him in the past 5 years have had an associated obstructive uropathy. What surprises me is not the fact that the lesion occurs, but that it has occurred so often in his series. This obvious discrepancy must have an explanation and there are three possibilities which come to mind.

The first is my own clinical ineptitude and I would be grateful to Dr. Block if he would refrain from commenting on that point. Number two is the possibility of a changing pattern of Crohn's disease for, after all, this has been a distinguishing feature of this entity over the past decade as we have been forced to alter our views of it from time to time. And the third, and I suppose the most likely explanation, is that Dr. Block and the University of Chicago group generally deal with much more severely ill examples of Crohn's disease than the rest of us do. This is perhaps evident by the high incidence of retroperitoneal perforation which they had.

My specific questions then are two. First, I would assume that you operated on a great number of similar instances prior to 1967 without recognizing this entity. What happened to those patients in terms of their urinary tract in subsequent years? Rephrased, have some of the patients on whom you operated—say, in 1960—without doing a ureterolysis subsequently returned to you with urinary problems?

The second question is: Do you think the rarity of this entity on the left side relates to the anatomy of the left side or do you think it relates to the intrinsic pathologic nature of granulomatous colitis when confined to the colon as opposed to the ileum?

Dr. William A. Altemeier (Cincinnati): Dr. Block and his associates also asked me to discuss this interesting paper and also kindly let me have a copy of it.

This presented a very interesting clinical entity of retroperitoneal disease secondary to Crohn's disease and characterized by cicatricial peri-ureteral fibrosis and ureteral obstruction in association with sinuses, fistulae or abscess which they found in the amazing number of 27 patients, as Alexander Walt has just indicated. We have had a more limited experience.

(Slide) In a study of 501 patients with intra-abdominal sepsis there were 203 patients that had retroperitoneal abscesses, or 38% of the overall number. Ninety-two or 17% were in the anterior retroperitoneal space with which we were concerned in this particular instance.

(Slide) This is part of a paper which was published in the *American Journal of Surgery* a few months ago on sources of intra-abdominal abscesses and note that regional enteritis or granulomatous ileocolitis accounted for three of the 501 patients or an incidence of six-tenths of one per cent.

(Slide) Notice in this anatomical drawing which we prepared in a paper published in 1961 on retroperitoneal abscesses, the proximity of the ureter as it crosses over the great vessels to the ileocecal region and it is not surprising that infections in this area that produce fibrosis will ultimately cause cicatricial stenosis of the ureter.

(Slide) The experience that we have had would be illustrated, I think, in these two cases. This is the abdominal x-ray of a young girl, 31 years of age, who had Crohn's disease and when I saw this flat film I was impressed with the fact that there was gaseous distention of the retroperitoneal spaces. there was also evidence of pneumatosis, cystoidus and testinalis in several places which was also relative to the granulomatous ileocolitis. At this time we did not appreciate the fact that she had an obstruction of her ureter.

(Slide) At operation, I removed the segment of the terminal ileum which was involved. This also included areas of pneumotosis, cystoides and testinalis and a previous ileo transverse colostomy that had been done in Seattle, Washington about 5 years before. This is the area of the anastomosis. During the dissection, it became apparent there was a fistula into the anterior retroperitoneal space and marked fibrosis and obstruction of the ureter. We freed up the ureter with some difficulty because of the entrapment of the ureter down deep in the pelvis. This area of continuing chronic infection with fibrosis of longstanding.

(Slide) In another patient, a young man of 21 years of age, who had had marked spasm of his right leg and a limp of 6 months, fortunately developed a septicemia and was referred to me for treatment of the septicemia. X-ray of the abdomen again showed the gaseous infiltration of the retroperitoneal space.

(Slide) On operation, we found a fistulous tract in the ileocecal segment that went into the anterior retroperitoneal space to produce a large abscess. There dense fibrosis around this abscess and again entrapment of the right ureter.

(Slide) In this instance, the abscess was drained. An ileocolectomy was done and a drainage also of the source abscess and notice the prompt response that was obtained.

I want to compliment Dr. Block and his associates for bringing us this interesting syndrome and its effective treatment to our attention. In addition, I want to ask Dr. Block about his ideas as to the etiology of chronic progressive retroperitoneal fibrosis, with obstructive uropathy and without Crohn's disease.

This was described by Dr. John Horman of Detroit in the late thirties when I was at Henry Ford Hospital and since then I have seen it in several of these patients and as far as we can tell, there has never been any relationship to Crohn's disease.

I want to point out also that we have seen this syndrome with actinomycosis, with longstanding appendicial abscesses, with dense fibrosis of the wall of the pelvis and the pan of the ileum in the right lower quadrant associated with tuberculosis and other fistulous tract diseases.

A word of caution: In dissecting out the ureter, if the ureter is densely entrapped in this thick, encased scar tissue, there is a risk not only of injuring the ureter, but also of injuring the femoral nerve which may not be easily identifiable in this dense scar.

Dr. George E. Block (Closing): The incidence of this lesion is certainly abnormal in our population. The 106 patients that I referred to are those patients who primarily had ileocolitis of the right side. These did not include those patients with predominently left sided ileocolitis which would have about doubled our personal operative experience.

Nevertheless, this is still a high percentage and I believe it is a reflection of the pattern of the type of patient who is referred to us with their longstanding, advanced and complicated disease.

Dr. Enker and I, in reviewing the literature in the last 10 or 15 years, have come across case reports of slightly over 70 patients in which this entity is described.

There is another point worthy of emphasis: this syndrome is the end stage of Crohn's disease or right sided ileocolitis with septic retroperitonitis that Dr. Altemeier so beautifully illustrated. That this represents end-stage ileocolitis poignantly emphasizes that this is an urgent indication for resection of the bowel disease *per se*.

As far as what happened to the patients prior to our recognition of this problem, the last two patients that were presented in the manuscript were patients who were recognized late in their course and suffered severe renal problems. The remainder were, I am afraid, merely undiagnosed.

Of interest in going through our patients with inflammatory disease, we were impressed with the infrequency of pyelograms that were conducted on a routine basis.

In the literature we note patients who have not had ureterolysis and there is a failure of relief in approximately 50% of the patients and, in a few reported patients, there was loss of renal function and even nephrectomy.

Interestingly, in other attempts at decompression of the ureter the patients averaged about three operations per patient in order to relieve the uretary obstruction.

The left-sided lesion has been recorded twice, to our knowledge. We believe this reflects both the anatomy of the retrocolic ureter and the fact that although Crohn's disease of the left side of the bowel and Crohn's disease of the right side of the bowel, if these are correct terms, are histologically identical, certainly from a pathogenic standpoint they are not.

Crohn's disease on the left side of the bowel, rarely penetrates, is rarely the site of the origin of the fistula and it is a real rarity to have a free perforation.

Therefore, retroperitonitis on the left side and its subsequent ureteral obstruction would be the expected rarity that it has proven to be.

I believe Dr. Altemeier's listing of the cause of retroperitonitis in his slide emphasized one of the important mechanisms of this syndrome; that is, the majority of the lesions that he presented—a suture line leak, appendicitis, etc.—are acute and sudden problems as contrasted to the chronicity associated with the fistulae, abscess and sinus tract of retroperitonitis in Crohn's disease.

The third entity in addition to the perforation and retroperitonitis has to be a chronic lesion to engender the cicatrix and Crohn's disease certainly does that.

As far as idiopathic retroperitoneal fibrosis is concerned exclusive of Crohn's disease, a minority have septic complications, particularly diverticulitis, cholecystitis and septic diseases of the upper extremities have been identified.

We, of course, like all others see patients taking a certain amount of ergot for migraine headaches but uniformly this has been bilateral.

We have not seen patients and our second illustrative patient pointed this out, whose obstructive uropathy reversed spontaneously without operative treatment as contrasted to the idiopathic retroperitoneal fibrosis associated with ergot or Sansert.

Carcinoma of the Extrahepatic Biliary Tract

WILLIAM P. LONGMIRE, JR., M.D.,* MICHAEL S. McARTHUR, M.D.,
ELIAS A. BASTOUNIS, M.D., JONATHAN HIATT, B.A.

From the Department of Surgery,
UCLA School of Medicine,
Los Angeles, California 90024

CARCINOMAS of the extrahepatic biliary system, although relatively rare, have a number of deceiving clinical features that make it important for abdominal surgeons to understand thoroughly their pathologic patterns, growth characteristics, and diagnostic difficulties:

1. Depending upon the site of origin of the tumor in the duct, local operative findings are very divergent. Tumors in the lower one-third of the duct produce biliary obstruction and marked dilatation of the entire proximal biliary system, including the gallbladder, unless it has been removed or has been the site of previous disease; tumors arising at the confluence of the hepatic ducts, however, although they also produce an obstructive type jaundice, are characterized by small, collapsed, relatively empty bile duct and gallbladder, while the liver is turgid and enlarged.
2. The tumors, particularly those in the hepatic ducts high in the hilum of the liver, are small, localized, and easily overlooked at operation. Local biopsies frequently do not obtain tumor tissue, and the specimens are misinterpreted to indicate that the duct obstruction is due to fibrosis and scarring.
3. The majority of bile duct tumors are slow-growing and metastasize by local extension rather than by widespread venous or lymphatic invasion.
4. Symptoms, until the advanced stage of the disease, are related solely to biliary obstruction, and reestablishment of adequate biliary flow, even though the tumor is not removed, provides surprisingly good palliation.
5. Finally, despite the ability to provide palliation to a number of these patients, long-term survivors and "cures" rarely are obtained by current methods of treatment except for those tumors in the distal one-third of the duct.

Anatomical Location of Tumors

The anatomical location of these tumors has been emphasized with regard to methods of treatment and prognosis of the lesion,[11] and the suggestion has been made[12] that the extrahepatic biliary system be divided roughly into three areas: (1) the upper region, including the left and right hepatic ducts, their confluence, and the common hepatic duct; (2) the common duct from the region of the cystic duct down to the pancreas; and (3) the intrapancreatic portion of the common duct, not including tumors of the ampulla of Vater.

Tumors Arising Near the Confluence of the Hepatic Ducts

Of the 500 site-specified bile duct tumors reviewed by Sako *et al.*,[16] 263 were located in the common hepatic, the left or right hepatic ducts, or their confluence. As stated, tumors in these sites present a major problem in diagnosis. In 17 of 23 cases reported by Whelton and associates[18] and nine of 13 cases recorded by Klatskin,[9] the cause of the biliary obstruction was not identified at initial operative biliary exploration for obstructive jaundice. Equally distressing, however, is the fact that once these small, highly localized tumors have been identified, current methods of treatment rarely, if ever, result in cure. The slow growth characteristics of the tumor, however, together with the fact that relief of biliary obstruction even without removal of the tumor may afford very adequate palliation for months, justify exploration in all cases without evidence of distant metastases. Sixteen of 41 patients treated by Warren and associates[17] with palliative procedures survived for more than 1 year, and one lived for more than 3 years. One of our patients survived for more than 6 years.

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25–27, 1973.

Supported in part by the James G. Greims Trust Fund and a Sabbatical Fellowship* from the Blalock Foundation.

With the early successful reports of hepatic lobectomy and radical tumor excision by Mistilis and Schiff[13] and Haynes and colleagues,[7] followed by the exhortation of Quattlebaum and Quattlebaum[14] for a more aggressive approach to the treatment of these tumors, and the continued recent successful hepatic lobectomy tumor excisions of Cady and Fortner,[4] Klippel and Shaw,[10] and Kelly,[8] many surgeons now are exploring ways to remove these tantalizingly small, localized tumors by more radical technics.

Tumors of Middle Region of the Ductal System

Small, well-localized tumors in the common duct from the region of the cystic duct junction down to the upper border of the pancreas may be treated by local excision and end-to-end anastomosis of the proximal duct to the gut. In the series collected by Sako *et al.*,[16] the common duct was the single most common site of origin (203 tumors), although it accounted for less than the total number of tumors arising from the various hepatic ducts. Eleven of the 77 malignant bile duct tumors reported by Warren *et al.*[17] were in the common duct above the pancreas. Seven patients were treated by resection and end-to-end anastomosis or hepaticoenterostomy, and six survived for more than 1 year and three for more than 3 years. In our previous report of 20 patients, two had survived local resection and duct-enteric anastomosis for 7 and 10 months.[11] When local excision is not feasible, palliation may be considered either by decompression of the biliary system at the hilus or by hepatic wedge resection and intrahepatic cholangiojejunostomy.

Tumors of the Distal Portion of the Common Duct

These tumors arise in the intrapancreatic portion of the common duct and generally are grouped clinically with the periampullary tumors. Differentiation of the tumor at operation, and even in the excised surgical specimen, from cancer of the head of the pancreas may be difficult. These tumors, however, because of their site of origin, produce jaundice early; they usually are small, localized about the common duct, and without widespread lymph node involvement. The proximal ductal system is markedly distended. In the series of 77 malignant bile duct tumors reported by Warren and associates,[17] 18 arose in the intrapancreatic common duct. Fifteen patients were treated by pancreaticoduodenectomy, nine of whom had survived for more than 1 year and two for more than 3 years at the time of their report. Of 65 patients undergoing pancreaticoduodenectomy for periampullary tumors at the UCLA Hospital, ten were diagnosed as having cancer of the common bile duct. Three of these patients were alive more than 6 years postoperatively, one for 13.5 years.[2] If widespread local growth or distant metastases contraindicate resection of tumors in this location, a suitable segment of dilated proximal duct often can be identified for palliative decompression of the biliary system. A choledochoduodenostomy or choledochojejunostomy performed in 70 patients with periampullary tumor has resulted in an average period of survival of more than 10.5 months.[2]

Anatomical Studies

To assist in planning operative approaches to the ductal system at and above the confluence of the common hepatic with the left and the right hepatic ducts, detailed dissections have been made of the extraparenchymal hilar structures in 30 normal human livers obtained at postmortem examination.[3] There are a number of excellent anatomical studies of the relationships and variations of the biliary duct, hepatic artery, and portal vein in the hepatoduodenal ligament, as well as detailed studies of the segmentalization of these structures and the hepatic veins within the parenchyma of the liver, but the relationships of these structures in the immediate extraparenchymal region have been somewhat neglected.

Variations of the hepatic arterial supply of the two lobes of the liver have been studied extensively. Daseler and co-workers[5] described the two most common patterns: (1) A single common hepatic artery, as seen in 83.2% of the cases, arose from the coelic axis and coursed in the left portion of the hepatoduodenal ligament as a long trunk that did not break up into its hepatic branches until it had come within 4 cm. of reaching the surface of the liver. At this point it branched into two main trunks, one to the right, the other to the left hepatic lobe. The cystic artery arose from the right hepatic artery. (2) The common hepatic artery was absent in 12.2% of cases, with the right and left lobes supplied by two separate vessels. The left hepatic artery arose from the coelic axis and supplied the left lobe. The right hepatic artery arose from the superior mesenteric artery and passed behind the duodenum to course up the right posterior border of the hepatoduodenal ligament to supply the right hepatic lobe and to give rise to the cystic artery.

The portal vein, a thick-walled vessel 6.5 cm. in length, regularly is formed by the junction of the splenic and superior mesenteric veins beneath the neck of the pancreas. It passes to the right and upward behind the superior portion of the duodenum to enter the liver at the right extremity of the porta hepatis. In its course it usually receives the superior pancreaticoduodenal vein and, in some instances, the coronary vein and an accessory pancreatic vein. High in the hilus is a single bifurcation into left and right branches. Its right branch is the usual site for the termination of the cystic vein.[6] The relationship of these branches, the divisions of the hepatic ducts above the common hepatic duct, and the branches of the hepatic artery formed the basis of our studies.[3]

As the common hepatic duct enters the tough fibrous tissue that covers the porta hepatis and enmeshes the branches of the ducts and vessels, it divides into its two main branches, the right and the left hepatic ducts, in more than 98% of cases.[5]

Division of the right hepatic duct into two or three intraparenchymal branches regularly occurs 1 cm. or less from the confluence of the main left and right hepatic ducts, one branch passing to the anterior superior segment, the other to the posterior inferior segment; a third branch to the caudate lobe is sometimes seen. The right hepatic artery regularly crosses over from the common hepatic artery on the left beneath the ductal system to lie on the dorsal surface of the right hepatic duct and send branches along its divisions. The portal vein lies posterior or dorsal to the duct and also sends branches to the same anatomical segments. The branches of these three structures enter the parenchyma by adjacent but not identical orifices.

By careful dissection of the tough fibrous hilar envelope, considerable lengths of these vessels and ducts to the left hepatic lobe can be isolated still outside of the true parenchyma of the liver. The structures cross in the bridge between the caudate and quadrate lobes and pass into the groove of the ligamentum teres.

It has been apparent to us at the operating table as we have attempted to dissect out the dilated left hepatic duct above a malignant or benign obstruction at the hepatic duct confluence that the dissection was limited laterally by a large branch of the portal vein that passed from its posterior or dorsal position in the hepatoduodenal ligament to cross the hepatic duct anteriorly or ventrally. This duct-venous relationship has been one of our particular interests.

Three general patterns of duct-vein relationship have been identified in the 30 livers studied. In the most common variety, which we have labelled Type A (22/30) (Fig. 1A), the duct runs slightly above and superficial to (cranio-ventrally) the left branch of the portal vein for a distance of 3 or more cm., the major division of the duct then passing beneath the portal vein to the lateral segment of the left lobe. A smaller division continues parallel with the portal vein into the cleft of the ligamentum.

In a much less frequent arrangement, Type B (4/30) (Fig. 1B), the major division of the duct continues its parallel course and passes superficial or ventral to the portal vein with, in some cases, a much smaller division passing beneath or dorsal to the vein at the left lateral margin of the hilar area. In four livers, labelled Type C (Fig. 1C), the proximal relationship of duct and vein from the confluence is the same as in the other two types. Laterally, however, the divisions passing beneath the portal vein and continuing parallel to it are of equal size. Three or four small ducts join the left hepatic duct within 2 cm. of the confluence and drain the caudate lobe. Small ducts from the caudate lobe may also enter the confluence or, at times, they may empty into the right hepatic duct.

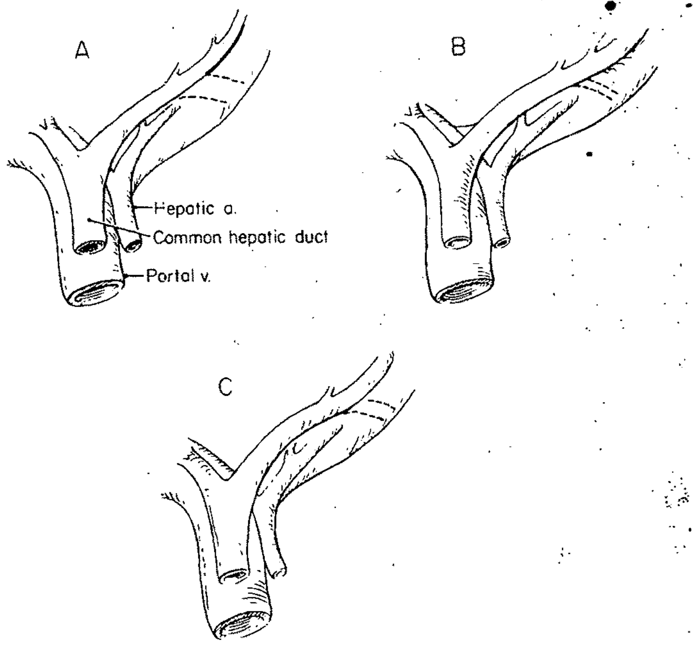


Fig. 1. Relationship of hepatic duct, artery, and portal vein above confluence. A. Major division of left hepatic duct passes beneath portal vein laterally. B. Major division of left hepatic duct passes parallel to portal vein. C. Lateral branches of left hepatic duct of equal size.

These tertiary ducts, although quite small (1 to 3 mm. in diameter), in their normal state become dilated and thick-walled in the face of chronic obstruction, and at least the branches that serve major hepatic segments are of sufficient size to be dealt with surgically.

In the cases of high duct resections and hepatic lobectomies previously reported (Table 1, Fig. 2), the left lobe was resected four times, leaving right intrahepatic ducts for anastomosis, and the right lobe was resected in two cases, leaving the left hepatic ducts to be anastomosed with the alimentary tract.

The left hepatic duct was the site of the tumor in seven of Warren's[17] 77 cases. The right hepatic duct was not the primary site in a single case. It is possible, however, that these cases would have been classified as intrahepatic duct tumors because the extraparenchymal right duct is so short.

TABLE 1. *Review of Literature*

Author	Area Liver Resected	Type of Duct-Enteric Anastomosis
Mistilis[13]	Left lobe	T-tube from common duct into Rt. hepatic
Haynes[7]	Left lobe	Rt. hepatic duct-jejunum Roux-en-Y
Quattlebaum[14]	Right lobe	Left hepatic duct-jejunum Roux-en-Y
Cady[4]	Left lobe	Rt. hepatic-common duct end-to-end
Klippel[10]	Right lobe	Left duct-jejunum Roux-en-Y
Kelly[8]	Left lobe	Rt. duct-end-to-side jejunum Roux-en-Y

Clinical Considerations

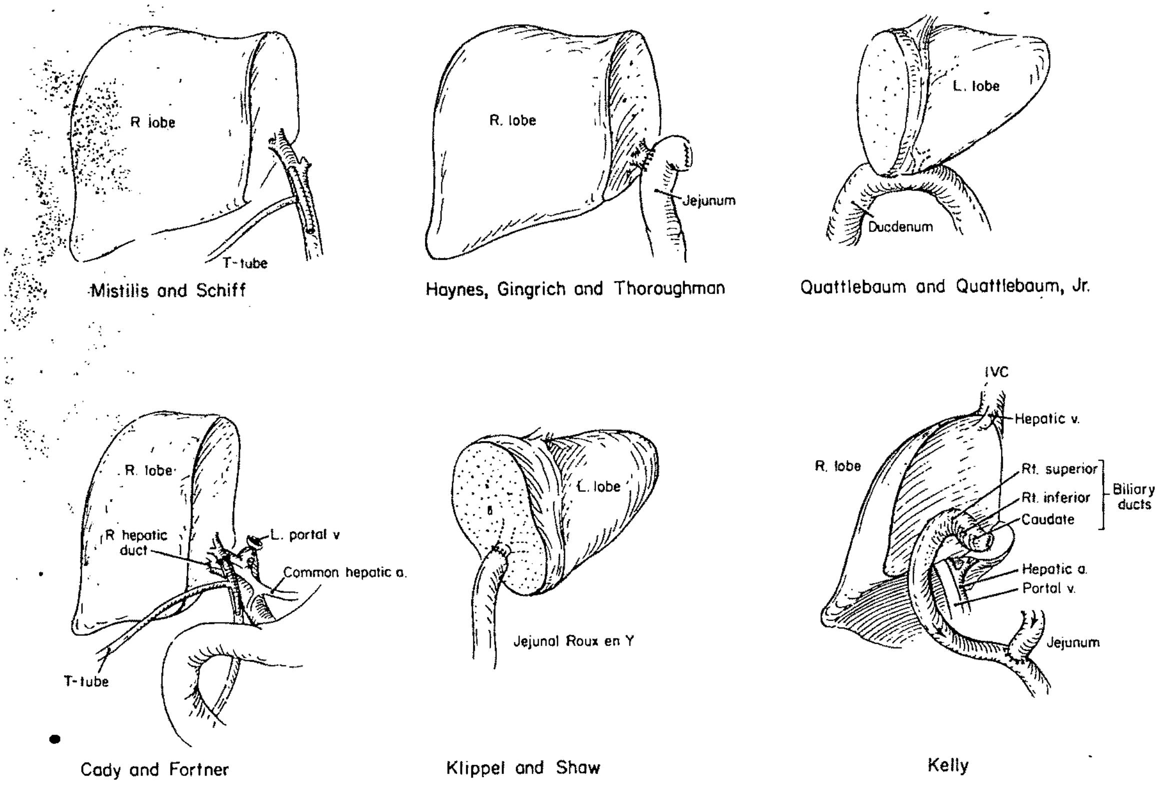
Despite the small, localized nature of these high-lying hepatic duct lesions, they frequently are found to be nonresectable. This is true not only when the entire extraparenchymal hilar biliary system is involved, but also when, in an otherwise resectable lesion, the hepatic artery and portal vein immediately adjacent are affected to the extent that an *en bloc* resection would devascularize major anatomical areas of the liver.

On the basis of our anatomical studies and the combined hepatic lobectomy-tumor excision procedures previously reported,[4,7,8,10,13,14] two possible operations have been planned that might increase the resectability of these tumors. A modification of one of these technics has been successfully performed.

(A) In tumors involving the right hepatic duct, the duct confluence, or both, with extension into hepatic artery and portal vein, it is proposed that a three-quarter hepatic resection be performed with removal of the right lobe and medial segment of left lobe. The proximal end of hepatic artery and portal vein are closed. The spleen is removed, and the splenic artery and vein are anastomosed to the branch of the hepatic artery and portal vein to the left lateral hepatic segment (Fig. 3). In one patient in whom a modification of this procedure was utilized, the left hepatic artery was situated so far to the left side of the hepatoduodenal ligament that it was not involved and, therefore, not resected. Mobilization of the proximal portal vein permitted an end-to-end anastomosis to the lateral segment branch after resection of the bifurcation of the portal vein with the specimen. The orifices of three dilated segmental ducts were anastomosed to the side of a Roux-en-Y jejunal limb to complete the reconstruction (Fig. 4).

Case Report

A 53-year-old man with a history of obstructive jaundice of 2 months' duration had been explored for biliary obstruction 3 weeks after the onset of jaundice. Biopsies of a thickened common hepatic duct were negative for tumor. After T-tube drainage of the common duct, there was a marked temporary improvement in his condition, but the jaundice subsequently recurred. At re-



Mistilis and Schiff

Haynes, Gingrich and Thoroughman

Quattlebaum and Quattlebaum, Jr.

Cady and Fortner

Klippel and Shaw

Kelly

FIG. 2. Types of major hepatic resections combined with hepatic duct carcinoma resections and reconstructions previously reported. Vascular supply to remaining hepatic lobe or segment not interrupted.

exploration 9 weeks after the first operation, a well-localized tumor at the confluence of the hepatic ducts was resected, together with the right lobe, the medial segment of the left lobe, the right branch of the hepatic artery, and the bifurcation of the portal vein. The stump of the portal vein was anastomosed to the portal vein branch to the left lateral segment. The left hepatic artery was not involved. Three dilated intrahepatic ducts in the lateral segment were anastomosed to the side of a Roux-en-Y jejunal limb. After a prolonged and diffcult postoperative course, he was discharged from the hospital with a slightly elevated but steadily declining serum bilirubin level (from 38 to 4.2 mg./100 ml.), normal stools, and increasing oral intake. On recent examination 1 month after discharge, the jaundice has continued to recede, and he has gained 13 lbs.

(B) Resection of the left lobe with interruption of the inflow blood supply might be accomplished by mobilizing the hepatic artery sufficiently (after division of the gastroduodenal branch) to anastomose it with the distal right hepatic artery, advancing the portal vein for end-to-end anastomosis to the right branch, as described on the left side (Fig. 5).

Because complete mobilization of the extraparenchymal left hepatic duct provides a longer segment of duct than does the much shorter right hepatic duct, it would seem to offer technical advantages for duct-enteric anastomosis after resection of the tumor and distal liver tissue, but this, of course, varies with the location of the tumor.

Case Material

Since 1955, 63 patients with the diagnosis of carcinoma of the bile duct have been seen at the UCLA Hospital. As in other reported series, the 36 male and 27 female patients have about a 3 to 2 ratio. The age range was 24 to 78 years, and the age distribution is shown in Figure 6.

Two-thirds of the patients queried had had no previous history of biliary tract disease. One-third gave a history of previous cholecystitis, cholelithiasis, or "trouble with the bile duct."

Symptoms

Gradual onset of jaundice was noted in more than 50 of the patients; only three patients were aware of an acute onset of their symptoms. Pain, present in one-third of the patients (21), was the second most common symptom, with weight loss, decreased appetite, and general malaise recorded in less than one-fourth of the patients. Evidence of cholangitis, as indicated by chills and fever, was recorded in only 7 of the 63 patients.

Symptoms seemed to be very similar, regardless of the anatomical location of the carcinoma. There was no significant difference in the mode of onset or the predominant symptoms in lesions of the proximal, middle, or distal thirds of the extrahepatic biliary system.

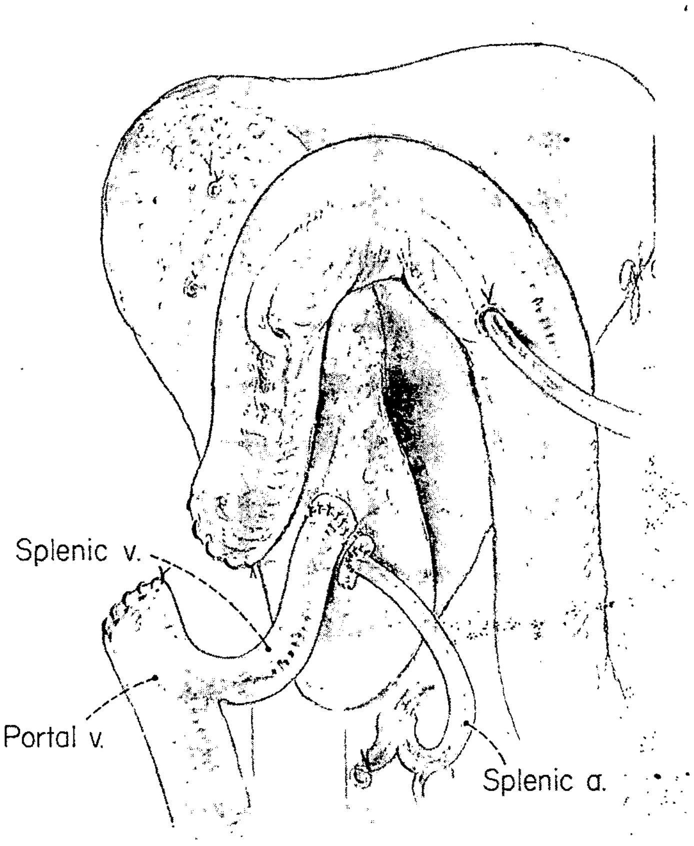


FIG. 3. Proposed operation for resection of carcinoma of right hepatic duct and confluence together with inflow blood supply of remaining left lateral segment.

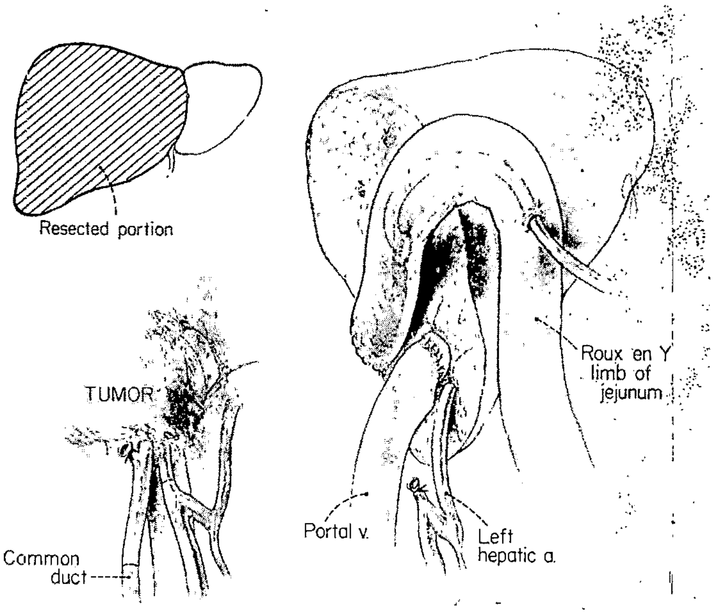


FIG. 4. Three-quarters hepatic resection with excision of carcinoma of right hepatic duct and confluence together with involved portal vein.

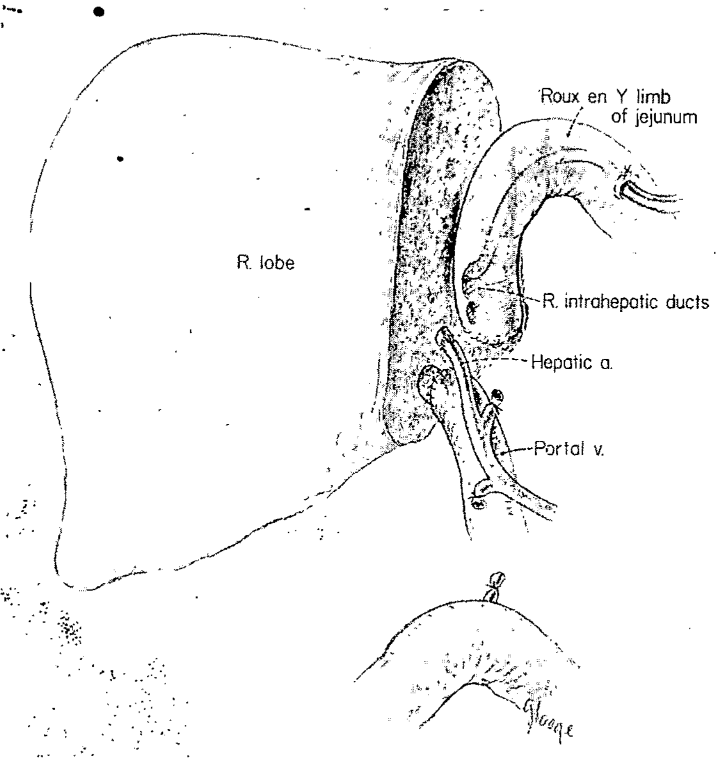


FIG. 5. Proposed operation for resection of carcinoma of left hepatic duct and confluence together with inflow blood supply.

Approximately one-half of the patients (33) consulted a physician within the first 3 months after onset of symptoms, and about one-half (32) received some definitive treatment within 4 months.

Diagnostic Studies

The hematocrit was less than 40%, and the white blood cell count was above 8,000 cu. mm. in one-half of the patients; prothrombin time was less than 80% in 20 of 49 patients tested.

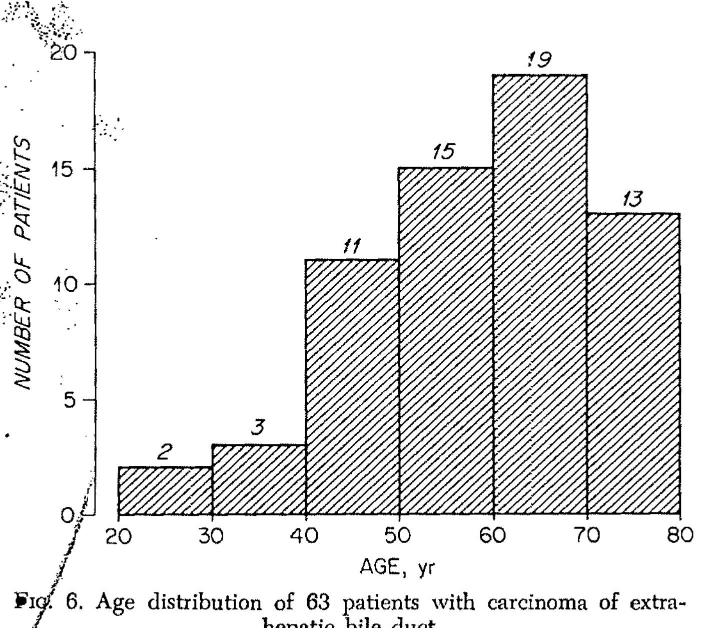


FIG. 6. Age distribution of 63 patients with carcinoma of extrahepatic bile duct.

The most helpful diagnostic test was the percutaneous cholangiogram. Pertinent diagnostic information was obtained for each of the 12 patients on whom the procedure was performed successfully. There were no positive contributory findings in the 15 upper gastrointestinal series completed. Radioactive liver scans were abnormal but not diagnostic in seven patients and normal in four. Arteriograms were also abnormal but not diagnostic in three patients and negative in two. When jaundice had been relieved by a preliminary operation or before jaundice became severe, an intravenous cholangiogram was abnormal in all six patients in whom ducts were visualized.

Classification and Treatment

Methods of treatment varied, depending upon the location of the tumor in the ductal system. Therefore, the 63 cases have been grouped into (1) upper one-third or confluence of hepatic ducts, 34 cases; (2) middle one-third, region of cystic duct down to pancreas, 13 cases; (3) lower one-third or intrapancreatic duct tumors, 13 cases; (4) extensive intraluminal papillary tumors, 3 cases.

Tumors of Hepatic Ducts (upper one-third tumors)

Thirty-four tumors in this series were situated at or very near the confluence of the right and left hepatic ducts with the common hepatic duct. Preliminary operations were performed on 25 patients; some underwent more than one procedure (Table 2). The true neoplastic nature of the obstructing lesion was identified by positive tissue biopsy in only eight patients. In the 17 other patients undergoing preliminary operations, a neoplasm was at times suspected but not proven, either because a biopsy was not taken or the biopsy did not contain tumor.

Concern for a definitive diagnosis of the obstructive jaundice, necessity of further treatment of the obstructing lesion, or incompletely relieved jaundice prompted the referral of these patients after the preliminary operation (Table 3). Some patients had more than one procedure; one patient died from a massive pulmonary embolus while awaiting operation.

Postoperative complications occurred in 16 patients. These were most frequently related to infection in the ductal system (cholangitis) or in the right subhepatic space or the wound; biliary fistulae; or bleeding from the upper gastrointestinal tract, usually occurring with sepsis. Seventeen patients did not have postoperative complications.

After operation there was relief of jaundice in 15 patients, partial relief in nine, and no relief in six patients.

Five patients died during the first month after operation of causes directly related to the procedure, and there were 23 late deaths (Table 4). Five patients are alive at 2, 3, 7, and 7 months and 4½ years after operation.

Middle One-Third Lesions

In 13 patients, the tumor was classified as occupying the middle one-third of the extrahepatic ductal system, this being considered roughly the region from the cystic duct down to the superior border of the pancreas.

Preliminary operations were performed on all 13 patients; some had more than one procedure (Table 5). Biopsies were attempted in five patients, and tumor tissue was identified in two. Secondary operations performed after referral are listed in Table 6.

Seven patients had postoperative complications, again usually consisting of biliary, peritoneal, or wound sepsis occurring at times with upper gastrointestinal hemorrhage. Six patients recovered without complications. Jaundice was relieved in 11 and partially relieved in two patients. Palliation was considered excellent in three, good in seven, and fair in one. There was one postoperative death at 1 month after operation. The other 12 patients died after the period of survival listed in Table 7.

Chemotherapy (intravenous 5-fluorouracil) provided symptomatic improvement for 4 months in one patient but was ineffective in a second patient.

Distal One-Third Lesions

In 13 patients, tumors were located in the intrapancreatic or distal one-third of the ductal system. Preliminary operations were performed in seven patients and are listed in Table 8. Secondary or definitive operations were performed in 11 of the 13 patients for further evaluation (Table 9). In two patients, secondary operative procedures were not indicated. There were no postoperative complications in seven patients. Non-fatal complications developed in four patients; two had wound infections, and two had intraperitoneal abscesses occurring with a biliary or pancreatic leak, one with hepatic coma.

Jaundice was relieved and the period of palliation was considered good or excellent in all 11 patients operated upon.

X-ray therapy helped to decrease pain in the one patient on whom it was performed. No response was noted from 5-fluorouracil injections in three patients. Eight of the patients have died (Table 10), and five patients are alive 1, 1, 2, 10, and 15 years after pancreaticoduodenectomy.

Papillary Tumors

Extensive intraductal papillary tumors were encountered in three patients. A preliminary operation was performed on one of these patients for the removal of a gangrenous acalculous gallbladder. The common duct was explored and a positive tumor biopsy obtained. At the definitive operation, positive biopsies were obtained in the other two cases. A choledochojejunostomy with a Roux-en-Y limb was performed in one case. T-tubes were inserted through tumor in the common ducts of the other two patients. Jaundice was relieved by the choledochojejunostomy. T-tube insertion relieved jaundice in one patient and gave partial relief in the other. Palliation was considered good in one and fair in two patients. One patient is alive 5 months after choledochojejunostomy. The other two are dead, one at 10 months, the other at 2½ years after T-tube insertion.

TABLE 2. *Preliminary Operations Performed*

Procedure	Number of Times Performed
Exploratory laparotomy only	7 (7)
Exploration common bile duct	15
Cholecystectomy	6
Duct-enteric bypass	1 (1)
Insertion of T-tube	14 (14)
Dilatation of obstruction + T-tube	2 (2)
Cholecystojejunostomy	1 (1)
Biopsy, positive	8
Biopsy, negative or omitted	17

Parentheses refer to number of times performed as principal procedure.

Hepatic Resection

Hepatic resection was performed in 13 patients as a part of a palliative operation to enable the creation of an intrahepatic biliary bypass or as a part of an operation for resection of the tumor.

TABLE 3. *Secondary and/or Definitive Operation Performed*

Procedure	Number of Times Performed
Exploratory laparotomy only	2 (2)
Exploration common bile duct	15
Cholecystectomy	4
Duct-enteric bypass	3 (3)
Insertion T-tube in duct	16 (11)
Dilatation duct insertion T-tube	2 (2)
Resection tumor, duct-enteric anastomosis	4 (4)
Rt. hepatic lobectomy, duct-enteric anastomosis	1 (1)
Hepatic resection, cholangiojejunostomy	8 (8)
3/4 hepatectomy, rt., duct-enteric anastomosis	1 (1)
Hepatic artery cannulation	1 (1)

Parentheses refer to number of times performed as principal procedure.

Partial resection of the left lobe (9 cases) or the right lobe (2 cases) followed by intrahepatic cholangiojejunostomy was generally ineffective as a palliative bypass

TABLE 4. *Period of Survival from Operation to Death*

Period	Number of Patients
0–3 mos.	11*
3–6 mos.	2
6–9 mos.	5
9–12 mos.	2
1–2 yrs.	6
2–3 yrs.	1
15 yrs.	1
Total	28

* Includes five operative (within 1 mo.) deaths

TABLE 6. *Secondary or Definitive Operations Performed*

Procedure	Number of Times Performed
Exploration common bile duct	3
Cholecystectomy	2
Insertion T-tube	4 (3)
Duct-enteric bypass	3 (3)
Resection tumor duct-enteric anastomosis	4 (4)
Hepatic resection, cholangiojejunostomy	3 (3)

Parentheses refer to number of times performed as principal procedure.

procedure. Severe postoperative complications consisted of one or more of the following and occurred in all but two patients: wound or intraperitoneal abscesses, biliary fistulae, gastrointestinal hemorrhage, and hepatic insufficiency. Five patients died within 30 days of causes directly related to the operative procedure. Four patients survived the operation 5 months or more, including one patient who died 2½ years after operation and one who is still alive at 4½ years.

Two conditions must be present for intrahepatic cholangiojejunostomy to be successful: (1) there must be free communication between the left and right intrahepatic ductal systems, and (2) the intrahepatic ductal system must be dilated. None of the eight patients with lesions in the upper one-third of the ductal system had free communications of the left and right intrahepatic ductal systems, a condition that probably accounts, in part, for the poor results obtained. Two of the three patients undergoing this operation for lesions of the middle one-third of the ductal system, with good communication of the left and right intrahepatic systems, received significant periods of palliation (9 months, 2½ years).

Two attempts have been made to combine major hepatic resection with resection of the tumor. One patient died 1 month after excision of the hilar tumor and left hepatectomy followed by an anastomosis of the stump of right hepatic duct to a Roux-en-Y jejunal limb. The second patient, described in detail in a previous section, is alive 8 months after resection of the hilar tumor and the right three-fourths of the liver, including the right lobe and the medial segment of the left lobe. The ducts of the lateral segment of the left lobe were anastomosed to a Roux-en-Y jejunal limb.

Discussion

Bile duct carcinomas in the distal one-third or intrapancreatic portion of the common duct must be differentiated from benign lesions such as impacted stones, chronic pancreatitis, and posterior penetrating duodenal ulcers. It usually is not possible at the time of operation to differentiate this tumor from the much more common carcinoma of the pancreas, but if benign conditions are ruled out and there is no evidence of cancer spread outside of the area to be resected, pancreaticoduodenectomy is indicated. A positive biopsy is comforting but not essential before embarking on this extensive procedure. The presence of tumor was confirmed in eight of our 11 patients with intrapancreatic bile duct tumors who had definitive operations. The important criteria in establishing the diagnosis and determining the resectability of bile duct tumors in this location are 1) the presence of local or disseminated tumor, 2) a negative history and absence at operation of cholecystitis and cholelithiasis, 3) the appearance of a generally dilated ductal system, and, most importantly, 4) visualization of

TABLE 5. *Preliminary Operations Performed*

Procedure	Number of Times Performed
Exploration common bile duct	5 (5)
Cholecystectomy	2
Insertion T-tube	6 (6)
Sphincterotomy papilla of Vater	1 (1)
Incision, drainage intrahepatic bile collection	1 (1)
Biopsy, positive	2
Biopsy, negative	3

Parentheses refer to number of times performed as principal procedure.

TABLE 7. *Period of Survival from Operation to Death*

Period	Number of Patients
1–3 mos.	1
6–9 mos.	2
9–12 mos.	2
1–2 yrs.	2
3–4 yrs.	2
4–5 yrs.	1
5–6 yrs.	2
11 yrs.	1*

* Patient died after removal of intrapancreatic recurrence of tumor 11 years after original tumor resection and choledochoduodenostomy.

the site of distal obstruction as demonstrated by percutaneous or operative cholangiography.

Tumors in the middle one-third or in the common hepatic duct must be differentiated from sclerosing choledochitis and, possibly, primary biliary cirrhosis. Sclerosing choledochitis unassociated with a disease such as ulcerative colitis or retroperitoneal fibrosis is rare. As Altemeier and associates[1] have indicated, the majority of such supposedly benign sclerosing obstructions eventually are proved to be primary bile duct carcinomas. Diffuse irregular narrowing and displacement of the duct as demonstrated by operative or percutaneous cholangiography suggests the proper diagnosis.

Tumors of the upper one-third involving the common hepatic duct, left and right hepatic ducts, and their confluence are the most easily overlooked of these tumors. They may be difficult to palpate or to see until the hilus of the liver is dissected extensively. An operative cholangiogram may be interpreted erroneously as entirely normal if free passage of the dye from the common duct into the duodenum is the only criteria sought; therefore, before a cholangiographic study is considered, complete free flow of dye into the left and right intrahepatic ductal systems also must be demonstrated. If necessary, the possible site of a high duct obstruction can be demonstrated by an operative cholangiogram made with the head of the operating table lowered and the hepatoduodenal ligament temporarily occluded with a non-crushing clamp distal to the point of dye injection. The dye can then be demonstrated to flow freely into the intrahepatic ducts or to be stopped at the hilus by an obstructing lesion. Percutaneous cholangiography is diagnostic of tumors when dilated intrahepatic ducts are demonstrated above a hilar obstruction; conversely, when intrahepatic ducts cannot be demonstrated on percutaneous cholangiography, the study is, unfortunately, nondiagnostic.

In the upper one-third region the two most important lesions to be differentiated are (1) primary biliary cirrhosis and (2) a benign sclerosing obstruction. A proper cholangiogram will rule in or out the possibility of an obstructing lesion. If no obstruction is present, a primary biliary cirrhosis is a strong possibility. A localized obstructing lesion, as previously indicated, usually is caused by a neoplasm.

The results of wide *en bloc* resection of bile duct tumors in the distal one-third demonstrate the effectiveness of this type of excisional treatment for primary bile duct tumors. Ten of the eleven patients operated upon with lesions in the distal one-third of the duct lived more than a year, and five of nine patients treated by pancreaticoduodenectomy are alive from 1 to 15 years after operation.

Resection of the tumor was possible in only four of the 13 patients with lesions of the middle one-third. Further resections were limited by involvement of the adjacent hepatic artery and portal vein in the hepatoduodenal ligament. These patients survived 1, 4, 5, and 11 years after resection.

TABLE 8. *Preliminary Operations Performed*

Procedure	Number of Times Performed
Exploration common bile duct	6
Cholecystectomy	1
Cholecystojejunostomy	2 (2)
Cholecystoduodenostomy	1 (1)
Insertion T-tube	4 (4)
Biopsy, positive	5
Biopsy, negative	2

Parentheses refer to number of times performed as principal procedure.

Three patients survived for more than 1 year after bypass procedures, and one is alive after 5 years. Thus, the results of both resection and of palliative operations for lesions of the middle one-third have been satisfactory and, at times, surprisingly gratifying.

Unfortunately, lesions occurring in the upper one-third, the site of more than half (34/63) of the tumors in our series, have been the most difficult to treat. Resection of the tumor was possible in only six patients, and in two of these it was necessary to combine a major hepatic resection with excision of the tumor. Eight of the patients who have died lived more than 1 year, one as long as 15 years. Five patients currently are alive, one 4½ years after operation. The most frequently utilized operation was the insertion of a T-tube (13/34) through the obstructed area of the duct. Five of the patients lived less than 3 months; however, five lived for 1 year or more. One patient lived for more than 2 years. Palliation by intrahepatic cholangiojejunostomy was attended by a high rate of postoperative complications and deaths. In general, the patients did not have the necessary ductal communications necessary for the success of this operation. Ragins and associates[15] recently reported 11 intrahepatic cholangiojejunostomy procedures for malignant biliary obstruction. The right lobe

TABLE 9. *Secondary or Definitive Operations Performed*

Procedure	Number of Times Performed
Duct-enteric bypass	1 (1)
Cholecystojejunostomy	1 (1)
Pancreaticoduodenectomy	9 (9)
Enteroenterostomy	1
Biospy, positive	6
Biopsy, not performed or negative	7

Parentheses refer to number of times performed as principal procedure.

TABLE 10. *Survival Period from Operation to Death*

Period	Number of Patients
6–9 mos.	1
9–12 mos.	2
1–2 yrs.	4
2–3 yrs.	1

was used four times, the left lobe seven times, and there were three postoperative deaths. Their surgical mortality rate was no worse for the procedure than for extrahepatic biliary bypass operations performed at their institution. The average survival time for four patients with carcinoma of the common bile duct who underwent intrahepatic cholangiojejunostomy was 14.3 months. A complementary gastrojejunostomy was recommended, and it was suggested that in those situations in which there is not free communication between the right and the left major hepatic ducts, a bilobal intrahepatic cholangiojejunostomy be considered.

We would agree with those authors who have suggested that an attempt be made in carefully selected cases of lesions at the liver hilus to extend the limits of resection to include major hepatic resections in an effort to achieve results comparable to those after *en bloc* resection of intrapancreatic bile duct tumors. Two operations have been proposed, one of which has been performed in a patient (Table 11, Case 13), that would permit resection not only of the duct and its tumor but also of the adjacent involved hepatic inflow blood supply and major segments of the hepatic parenchyma. In a second patient (Table 11, Case 12), a left lobar hepatectomy with excision of duct carcinoma and hepaticojejunostomy was performed; however, the blood supply to the remaining lobe was not interrupted. Our anatomical studies of the extraparenchymal hilar structures and their relationships have emphasized the extended segment of extraparenchymal left hepatic duct that is available for anastomosis above the confluence of the left, right, and common hepatic ducts.

Summary

A series of 63 patients with primary bile duct carcinomas seen at the UCLA Hospital since 1955 have been analyzed and divided into four groups, depending upon the site of the tumor in the extrahepatic ductal system. More than half of the tumors occurred in the upper one-third, while the other half was about equally divided between those occurring in the middle and lower thirds of the extrahepatic duct system. Three widespread intraluminal papillary tumors have been placed in a special category.

The signs and symptoms of bile duct tumors are very similar in all regions; however, the operative findings and the treatment differ, depending upon their location. The difficulties of establishing a correct diagnosis at the time of operation are again demonstrated in this series. Due to the slow growth characteristics of many of these tumors, extended periods of palliation resulted from a

TABLE 11. *Hepatic Resections*

Case	Procedure	Location of Tumor	Complication	Period of Survival
1	Partial left hepatectomy cholangiojejunostomy bypass	Confluence hepatic ducts	Sepsis, coma	1 mo.
2	Partial left hepatectomy cholangiojejunostomy bypass	Confluence hepatic ducts	None	4-1/2 yrs. alive
3	Partial left hepatectomy cholangiojejunostomy bypass	Confluence hepatic ducts	Cholangitis, biliary fistula	2-1/2 wks.
4	Partial left hepatectomy cholangiojejunostomy bypass	Confluence hepatic ducts	G. I. hemorrhage	2 wks.
5	Partial left hepatectomy cholangiojejunostomy bypass	Confluence hepatic ducts	Sepsis, pelvic abscess	3 mos.
6	Partial left hepatectomy cholangiojejunostomy bypass	Confluence hepatic ducts	None	2 mos.
7	Partial left hepatectomy cholangiojejunostomy bypass	Middle 1/3	Sepsis, G. I. hemorrhage	1 mo.
8	Partial left hepatectomy cholangiojejunostomy bypass	Middle 1/3	Mild cholangitis	2-1/2 yrs.
9	Partial left hepatectomy cholangiojejunostomy bypass	Middle 1/3	Mild G. I. hemorrhage	9 mos.
10	Partial right hepatectomy cholangiojejunostomy bypass	Confluence hepatic ducts	Abdominal abscess	5 mos.
11	Partial right hepatectomy cholangiojejunostomy bypass	Confluence hepatic ducts	Cholangitis, wound infection, G. I. hemorrhage	1 mo.
12	Left hepatectomy Right hepatic duct-jejunum	Confluence hepatic ducts	Sepsis, H. I. hemorrhage	1 mo.
13	3/4 hepatectomy, right Left hepatic duct-jejunum	Confluence hepatic ducts	Sepsis, hepatic failure, biliary fistula	7 mos. alive

variety of procedures designed to bypass the obstruction in the biliary tract. The most commonly used palliative procedure has been the insertion of a tube into the duct that passes above and below the tumor through the site of obstruction.

The tumors are generally small, well-localized, and frequently slow-growing. Tumors in the lower one-third of the duct may be treated by radical *en bloc* resection (pancreaticoduodenectomy) and offer the best prognosis, both for long-term palliation and cure.

More than half of the tumors in this series were located at or near the confluence of the hepatic ducts, and resection of the tumor was attempted in only six of 34 cases. It is possible that, were procedures available that would permit a more extensive *en bloc* resection of tumors in the middle and upper thirds of the duct system, the period of palliation might be extended and more "cures" obtained. Such procedures must take into account that these small tumors often are not amenable to resection by present methods, not only because of their difficult position in the ductal system, but equally as well because they involve the critically important hepatic inflow blood supply. Detailed anatomical studies of the hepatic ducts, arteries, and portal veins at the hilus support the concept of combining extended hepatic resection with tumor excision and including segments of the hepatic blood supply in selected patients with tumors in the upper one-third of the duct. Operative procedures for resection of the right and left lobes have been proposed. One such operation has been performed; in a second patient, hepatic lobectomy and tumor excision were performed without interruption of the blood supply to the remaining lobe.

References

1. Altemeier, W. A., Gall, E. A., Zinninger, M. M. and Haxworth, P. I.: Sclerosing Carcinoma of the Major Intrahepatic Bile Ducts. Arch. Surg., 75:450, 1957.
2. Aston, S. J. and Longmire, W. P., Jr.: Pancreaticoduodenal Resection: Twenty Years' Experience. Arch. Surg., (In press).
3. Bastounis, E. A., Hiatt, J., McArthur, M. S. and Longmire, W. P., Jr.: Anatomy of the Hepatic Hilum. (Submitted for publication.)
4. Cady, B. and Fortner, J. G.: Surgical Resection of Intrahepatic Bile Duct Cancer. Am. J. Surg., 118:104, 1969.
5. Daseler, E. H., Anson, B. J., Hambley, W. C. and Reimann, A. F.: The Cystic Artery and Constituents of the Hepatic Pedicle. Surg. Gynecol. Obstet., 85:47, 1947.
6. Douglass, B. E., Baggenstoss, A. H. and Hollinshead, W. H.: The Anatomy of the Portal Vein and its Tributaries. Surg. Gynecol. Obstet., 91:562, 1950.
7. Haynes, C. D., Gingrich, G. W. and Thoroughman, J. C.: Carcinoma of the Bile Duct. Am. Surg., 30:578, 1964.
8. Kelley, K. A.: Successful Resection of Adenocarcinoma of Junction of Right, Left, and Common Hepatic Biliary Ducts. Mayo Clin. Proc., 47:48, 1972.
9. Klatskin, G.: Adenocarcinoma of the Hepatic Duct at its Bifurcation within the Porta Hepatis. Am. J. Med., 38:241, 1965.
10. Klippel, A. P. and Shaw, R. B.: Carcinoma of the Common Bile Duct: Report of a Case of Successful Resection. Arch. Surg., 104:102, 1972.
11. Lippman, H. N., McDonald, L. C. and Longmire, W. P., Jr.: Carcinoma of the Extrahepatic Bile Ducts. Am. Surg., 25:819, 1959.
12. Longmire, W. P., Jr.: Discussion of Paper by Quattlebaum and Quattlebaum. Ann. Surg., 161:888, 1965.
13. Mistilis, S. and Schiff, L.: A Case of Jaundice due to Unilateral Hepatic Duct Obstruction with Relief after Hepatic Lobectomy. Gut, 4:13, 1963.
14. Quattlebaum, J. K. and Quattlebaum, J. K., Jr.: Malignant Obstruction of the Major Hepatic Ducts. Ann. Surg., 161: 876, 1965.
15. Ragins, H., Diamond, A. and Meng, C-H.: Intrahepatic Cholangiojejunostomy in the Management of Malignant Biliary Obstruction. Surg. Gynecol. Obstet., 136:27, 1973.
16. Sako, S., Seitzinger, G. L. and Garside, E.: Carcinoma of the Extrahepatic Bile Ducts. Review of the Literature and Report of 6 Cases. Surgery, 41:416, 1957.
17. Warren, K. W., Mountain, J. C. and Lloyd-Jones, W.: Malignant Tumors of the Bile Ducts. Brit. J. Surg., 59:501, 1972.
18. Whelton, M. J., Petrelli, M., George, P., Young, W. B. and Sherlock, S.: Carcinoma at the Junction of the Main Hepatic Ducts. Quart. J. Med., 38:211, 1969.

Discussion

Dr. William H. ReMine (Rochester): I think this is a most significant paper. It's true this is a very rare condition, fortunately, because it's a lethal problem and it involves very complex anatomy. anatomy.

The rarity of it was exhibited a number of years ago by Dr. Walters at our institution when he and Neibling reviewed our experience there and found 90 cases of extrahepatic biliary tract carcinoma, of 22,000 biliary tract procedures. Macklin also found in a review of autopsy material, that there were five cases in 9,000.

I believe this is a procedure that should be dealt with by members of this organization, or similarly trained persons and not by just the casual operator.

This slide is from work by Mongé and Judd from our institution to show how difficult it is to obtain a long-term survival for this problem. We have nine cases—of 239 pancreatic duodenectomies that were performed for carcinoma in the lower end of the common duct, there was one long-term survivor.

Our emphasis should be directed towards the diagnosis of this condition to attempt early repair of the problem or removal of the lesion. Judicious use of percutaneous transhepatic cholangiography, in our experience, has been somewhat helpful; not always as helpful as we would like it to be, but at least it gives us a clue. Our use of liver scans and angiography have not been as helpful as we would like. They have given us very little to go on. I think whenever there is a question about it, if we expect to do much for these people, they should be operated upon as early as possible.

I would like to congratulate Dr. Longmire on their attempt to develop an orderly technic as an approach to these problems. Perhaps those of us who have seen and heard the presentation will think about it for awhile, perhaps we may get a few more palliative results and maybe a few more cures. Dr. Walters pointed out a number of years ago that since these are low grade lesions, they grow slowly; that even an attempt at palliation can be very helpful and at that time he reported the case of one patient that lived 4½ years after a bypass type of procedure.

Dr. Kenneth W. Warren (Boston): This paper by Dr. Longmire and his associates covers a diffcult surgical problem superbly. I find it rather difficult, despite a moderate experience in the treatment of carcinoma of the bile ducts, to add to what they have said and even to disagree substantially with their basic conclusions.

Dr. Braasch, Dr. Ross and I recently reviewed the records of 103 patients with carcinoma of the proximal bile ducts at the Lahey Clinic over a 15-year period. Previously we had reported 26 pancreaticoduodenal resections for carcinoma arising in the distal common duct in which 36% of the patients suitable for 5-year results lived 5 years or longer. Our experiences with cancer in the proximal segment of the bile ducts, on the other hand, parallel very closely those of Dr. Longmire. Of 103 proximal carcinomas, three arose in the left hepatic duct, four in the right hepatic duct, 46 at the confluence of the two ducts, 24 occurred in the common hepatic duct and 15 at the junction of the cystic with the common hepatic duct and only eight in the supraduodenal segment of the common duct. All of these were adenocarcinomas; 66 were moderately well differentiated tumors and 35 were poorly differeniated tumors.

Although the mean survival of the two groups was similar, based on the histologic difference, only one patient with a poorly differentiated cancer was alive and well 5½ years after removal. Conversely, of the patients with well differentiated histologic tumors, one died 4½ years, one 7 years and two 9 years after operation. Two are alive with evidence of persistent disease, 4 and 6 years respectively, and two are alive 5 and 6 years without symptoms.

The relationship of the type of procedure employed and the long-term palliation or cure, with some exceptions, was essentially as follows: The resection of the tumor by a pancreatoduodenal resection, by segmental excision, or by a partial hepatectomy or hepatic lobectomy gives the best results. Unfortunately, as Dr. Longmire pointed out, these tumors all too frequently are at the confluence of the right and left duct and these radical procedures are not always possible. It is for that reason that we welcome the recommendation that he has made with respect to these tumors and we shall follow carefully the long-term results.

The next best results are obtained by bypass, either choledocho- or hepatocho-enterostomy over a T-tube, a Y or a modified Y tube. The dilatation and intubation with the T-tube a Y or a modified Y-tube, may, as pointed out, give long-term palliation. The creation of external fistulae on the other hand gives the highest mortality and the least salvage. Three of five patients in whom only a biopsy was performed in our group of patients lived 1 year longer.

In summary our experience has been very much like Dr. Longmire's. Earlier diagnosis would be helpful and perhaps extending the radical operation will have some application in the carefully selected patient.

Dr. W. Clayton Davis (Omaha): I would like to emphasize just one aspect of this excellent study of primary bile duct carcinoma.

Altemeier, Klatskin and now Longmire and a few others have emphasized the failures to diagnose adenocarcinoma at the bifurcation of the hepatic duct. Most often this is called sclerosing cholangitis.

(Slide) Over the last 9 years, I have seen 11 patients who proved to have carcinoma of the hepatic duct bifurcation after carrying the diagnosis of sclerosing cholangitis for long periods and after several operative biopsies.

Until surgeons and pathologists question the existence of a specific disease entity, that is, sclerosing cholangitis, it is improbable that many of us will take an aggressive approach in this region and therefore the beautiful treatments outlined by Dr. Longmire and his co-workers will not be applied as often as they could be.

Dr. William A. Altemeier (Cincinnati): Carcinoma of the bile duct is a relatively rare but serious and challenging lesion. Dr. Longmire and his group's experience with 62 patients seen since 1965 is truly remarkable, and their report with its anatomical studies and operative recommendations for surgical procedures should be helpful to all of us who practice abdominal surgery.

The information regarding the anatomical variations and the relationship of the biliary duct to the hepatic artery and portal vein are particularly helpful in this area because of the dense scarring that is usually associated with these carcinomas at that level.

Our experience with the lesion has also been recently summarized, and the complications of these carcinomas which not infrequently remain localized for long periods are related to obstructive jaundice, biliary cirrhosis, perihilar cicatrization, and infection. The usual cause of death is either infection, uncontrolled sepsis, or hepatic failure.

The extreme degree of emaciation developed by these patients is depicted in this slide. This patient had a carcinoma of the left main hepatic duct which I resected, and I believe he is the first case shown on Dr. Longmire's table since it had been reported by Doctor Schiff and Dr. Mistillis. He lived for 2½ years after a left lobectomy.

I cannot emphasize or re-emphasize more the comments that Dr. Longmire and the discussers have made of the value of early and definitive diagnosis of this lesion. The best method in my experience has been by transhepatic cholangiography.

This transhepatic cholangiogram was obtained in a patient who had a carcinoma of the left hepatic duct. It was resectable with a left lobectomy and was the second patient in whom I have done a left lobectomy. He is still living 3½ years after operation. The surgical specimen of this lobectomy shows the carcinoma still localized but close to the line of resection.

Lesions of the lower third of the common duct are much harder for us to recognize because usually they are associated with diseases of the gallbladder, evidence of pancreatitis, or some other lesion which clouds the diagnosis. Such was the case in this diabetic patient with a gangrenous gallbladder and pericholecystic abscess who was also found to have an apple core lesion of the lower third of the common duct. (Slide)

The last slide emphasizes the point that the last discusser made concerning the close similarity of this lesion to sclerosing cholangitis.

Pathologists may interpret this pseudoductal proliferation of these tumors as a benign process. If you have a problem, the AFIP may be helpful in arriving at a definitive diagnosis of sclerosing carcinoma, if one is present.

I want to compliment again the authors for their excellent and informative paper. I would like to ask them how often biopsies of these lesions are given an equivocal or wrong diagnosis by their pathologist. I would also like to ask how many of the patients were diagnosed as having sclerosing cholangitis only to be determined later to be sclerosing carcinoma of the bile ducts.

Dr. Robert C. Hickey (Houston): For many years we have admired the studies of Dr. Longmire and his colleagues on this general problem. I believe our admiration has increased today.

Dr. David Harshaw of the Downstate Medical Center in New York and I have some data from the Anderson Hospital that we would like to share with you. And, I have four slides.

The first slide shows in a smaller (22) number of patients, in a background interestingly enough of 100,000 patients with cancer, the distribution of carcinoma of the extrahepatic biliary duct system. It is quite similar. There are certain observations which can be made in this group of patients. Namely, number one, that they are usually operated upon prior to the time they are sent to a referral center. Secondly, as Dr. Altemeier has said, death is due to liver failure and infection. Cancer, as we know cancer, does not cause death.

The age of these patients is about 60 years as an average, but the spread in our group is from 22 to 79. In this group of patients we have had a median survival overall of 6 months; average of 10½ months.

The therapy that we are directing our attention toward is decompression of the liver. At times nature performs some very interesting experiments. We have had one patient who lived longer than the average and seemingly had done well with high energy 22 MeV therapy, but at the time of autopsy an anomalous duct had decompressed the liver into the gallbladder bed, and thus the patient's life was extended. Death finally occurred when the cystic duct and common duct juncture became blocked by cancer.

We have turned our attention to an operative procedure—originally, we had thought this was original with us but we have found this described in the literature by Smith (Smith, R, *Surgery of Gall Bladder & Bile Ducts,* Edited by Smith & Sherlock, Butterworth, Washington, D. C.)

Using primates in an attempt to develop an experimental model, we have placed an Ameroid ring, around the common duct and as the casein swells gradually an occlusion occurs, simulating cancer.

This slide shows the dilatation of the extrahepatic ducts, as one would view it at the end of 12 days. The next slide shows the anastomosis and decompression procedure that is carried out. You can see the common duct tied off here, then an opened subvesicle duct decompressing via the gallbladder bed, thence from the gallbladder into the gut through the Roux-en-T anastomosis.

We have had 3 primates that have lived 3 years, and are in good health, with this procedure.

Dr. William I. Wolff (New York City): I would like to address myself to the diagnostic aspect of this disease so beautifully demonstrated by Dr. Longmire in his operative dissections.

The key to surgical treatment for this lesion, a slowly growing tumor which extends and propagates along the biliary ducts, is early and accurate anatomical diagnosis.

Dr. Altemeier has shown you some very beautiful demonstrations of transhepatic cholangiography. We have found that the combined use of endoscopy, cannulation of the ampulla of Vater and retrograde visualization of the biliary ducts, plus transhepatic cholangiography can delineate with a reasonable degree of accuracy the precise anatomical location and extent of these lesions and perhaps bring a larger number of these patients to operation at an earlier date.

Dr. Michael S. McArthur (Closing): We thank the discussants for their comments. In particular, Dr. ReMine, Dr. Davis, Dr. Hickey and Dr. Wolff, for joining with us in re-emphasizing that an all-out effort at preoperative diagnosis should be undertaken.

Dr. ReMine, in our institution, also, percutaneous cholangiography was the most accurate preoperative diagnostic procedure.

Dr. Warren, we thank you for adding your extensive experience to that which we presented.

Dr. Altemeier, in regard to operative diagnosis, we had biopsy proven carcinoma in only a third of the patients at the time of the first procedure.

We would like to point out that our anatomical dissections were limited to 30 cases, but in those we paid particular attention to the bile ducts at the site of emergence from the liver parenchyma down to the confluence of the right and left hepatic duct, and in particular, this relationship to the surrounding vessels.

The first slide reveals the three types found.

Type "A," the most common type, revealed a left hepatic duct which divided, sending its major branch beneath the left branch of the portal vein.

In type "B" the left hepatic duct sent its major branch parallel to the portal vein, and in Type "C" the left hepatic duct divided into two separate and equal branches.

A review of the literature revealed six cases of extended hepatic lobectomy for carcinoma of the extrahepatic biliary tree with a biliary duct anastomosis. However, in our case as Dr. Longmire has pointed out, we were prepared to perform an *en bloc* resection of the tumor, the bile duct, hepatic artery and the portal vein. In our patient it was not necessary to resect the hepatic artery and this patient is alive and well 11 months postoperatively.

Our results with left hepatic lobectomy and intrahepatic choledochojejunostomy for carcinoma of the intrahepatic ducts has not been satisfactory. This is due in part to the common occurrence of the lack of communication between the right and left ductal system, due to the primary invasive nature of the tumor. With the systems obstructed, a left hepatic anastomosis drains only a small part of the left lobe.

The second slide shows our experience with this procedure and, in particular, note the frequency of severe complications. The third slide is a continuation of this experience.

We feel that to be effective there must be communication between the right and left dilated systems. The most promising situation is when the tumor arises in the middle third of the common bile duct, and communication between the right and left lobes still exists.

Of three instances in which this was followed, one patient survived 2½ years and another for 9 months.

Our approach to the management of these tumors is influenced by the fact that most of them grow slowly involving surrounding structures by direct spread, rather than by blood borne or lymph borne metastases and that the tumor may be quite small when symptoms of biliary obstruction first appear.

Each case must be individually assessed with a view to performing an *en bloc* resection with the hope of curing the tumor or of providing an extended period of palliation with relief of jaundice and freedom of pain and a general feeling of well-being.

Reasonable Surgery for Rhabdomyosarcoma:

A Study of 67 Cases

JAMES W. KILMAN, M.D.,* H. WILLIAM CLATWORTHY, JR., M.D.,**
WILLIAM A. NEWTON, JR., M.D.,*** JAY L. GROSFELD, M.D.†

From the Divisions of Pediatric Surgery and Thoracic Surgery, Department of Surgery, and the Department of Pathology, The Ohio State University College of Medicine, and The Columbus Children's Hospital, Columbus, Ohio and the Division of Pediatric Surgery, Department of Surgery, Indiana University School of Medicine, Indianapolis, Indiana

RHABDOMYOSARCOMA is the most common soft tissue sarcoma seen in infants and children. This tumor has a propensity for local recurrence and the patients usually die with distant metastases. In the therapy of nephroblastoma (Wilms' tumor) in children, it has been found that prophylactic radiation therapy and chemotherapy can control local disease and protect from metastatic disease which also occurs in these tumors. In an effort to achieve similar favorable results in rhabdomyosarcoma the use of *prophylactic* chemotherapy and radiation therapy was instituted in 1965 at The Columbus Children's Hospital. Prior to 1967, 29 children with rhabdomyosarcoma were seen at this institution and treated by a variety of methods including conventional radical surgery. In these patients 58% (17 of 19) died within 1 year of diagnosis and only 14% (4 of 29) survived for 5 years. With this dismal experience in mind, a planned protocol for the management of patients with rhabdomyosarcoma was established at this institution. This program consisted of (1) complete removal of the tumor if possible and re-resection if indicated at a later date; (2) radiation with a corrected for age tumor dose to the primary site and known metastatic site; (3) prophylactic chemotherapy consisting of repeated cycles of actinomycin D and vincristine sulfate initiated in the immediate postoperative period and persisting for 1 year. Since the adoption of this mode of therapy, 38 patients have been treated for rhabdomyosarcoma. Thirty-one of these have been treated by the established protocol method and 28 have survived (81% survival rate). These observations suggest that the use of prophylactic chemotherapy and local radiation therapy similar to that employed for the management of Wilms' tumors when combined with *reasonable* surgical treatment will result in excellent survival rates and less destructive and disfiguring operations in the future.

Clinical Experience

This study concerns 67 infants and children who have been treated at The Columbus Children's Hospital from the years 1948 through 1972. There were 35 boys and 32 girls in this series. A previous report from this institution in 1969 concerned 42 of these cases.[6] No patients have been lost to follow-up and this review concerns all of the patients treated prior to November of 1972. The use of prophylactic chemotherapy and radiation therapy similar to that employed in Wilms' tumors was initiated at The Columbus Children's Hospital in 1965. Previously, these patients had been managed in a variety of ways including radical surgery, some radiation therapy and

---

Read at the American Surgical Association Meeting of 1973, at Los Angeles, California, April 25–27, 1973.

Reprint requests: James W. Kilman, M.D., 410 West 10th Avenue, Columbus, Ohio 43210.

* Division of Thoracic Surgery, Ohio State University College of Medicine.

** Division of Pediatric Surgery, Ohio State University College of Medicine.

*** Department of Pathology, Ohio State University College of Medicine.

† Division of Pediatric Surgery, Indiana University School of Medicine.

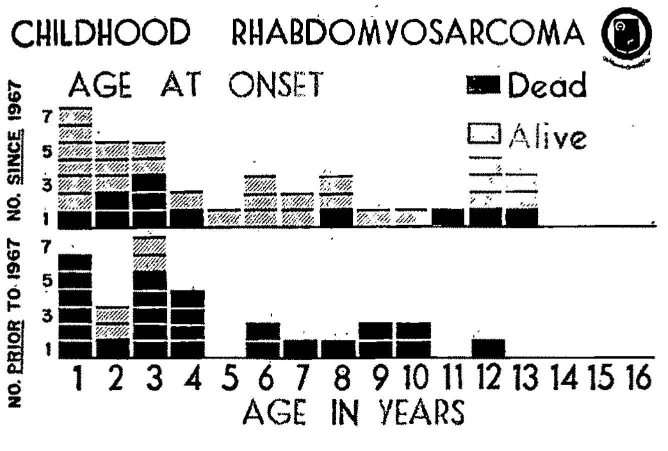


FIG. 1. Age of onset in this series of patients. Note that six of seven infants are alive after use of protocol therapy and that there are survivors regardless of age at the time of diagnosis of the tumor.

the sporadic use of palliative chemotherapy. In 1967 a planned treatment protocol was developed in conjunction with Children's Cancer Study Group A.[3] This consisted of initial and complete removal of all gross tumor; radiation therapy with a corrected-for-age tumor dose usually 2500 to 4000 rads to the primary site and prophylactic cyclic chemotherapy with actinomycin D and vincristine sulfate (more recently cyclophosphamide has been added as recommended by the Study Group). Our case material has been analyzed and the results achieved in patients treated prior to the establishment of this 1967 treatment protocol have been compared with those patients managed on the established protocol since 1967. Such variables as the age of the patient at the time of primary diagnosis, the stage of the disease as indicated by the surgeon at the time of primary diagnosis, the site of the tumor, the specific cell type of rhabdomyosarcoma and the type of surgical therapy given to each of these patients have been evaluated.

Age

Rhabdomyosarcoma has occurred in this series of patients from as early as 3 weeks of age to 14 years of age. One-third of the 67 cases were under 2 years of age. Prior to 1967 there were no survivors when the tumor was diagnosed under 1 year of age. Since the establishment of the protocol, the majority of these infants (6 of 7) are surviving. Similar good results are being observed in the older childhood group (Fig. 1).

State of Disease

All patients have been grouped according to the stage of their disease as determined by the surgeon at the time of original diagnosis. Stage I represents localized disease; Stage II represents tumors with local extension or with regional lymph node involvement; and Stage III includes patients with disseminated or metastatic involvement at the time of primary diagnosis (Table 1). It can be observed that survival was only possible in Stage I disease prior to the adoption of protocol therapy. Since 1967 and the use of radiation and prophylactic chemotherapy in addition to operation, there has been an 86% survival rate in Stage I disease and a 58% survival rate in Stage II disease. The survival rate in Stage III or disseminated disease is still dismal and we have had no survivors if the tumor was found to be wide-spread at the time of diagnosis.

Cell Type

The tumors have been grouped as to cell type by the classification as proposed by Horn and Enterline in 1958 including three main cell types: alveolar, embryonal and pleomorphic[7] (Table 2). Prior to 1967, cell type seemed to be an important factor in survival and there was a 60% survival rate with alveolar types of rhabdomyosarcoma although the majority of the rhabdomyosarcomas were of the embryonal variant. Since 1967, the majority of the tumors have been classified as embryonal and it is interesting to note that the cell type no longer seems to be an important factor in survival. The recent rates have been approximately the same for patients with all three cell types.

Tumor Site

The distribution of the primary tumor site in this series of patients is summarized on Figure 2. Rhabdomyosarcomas more commonly arise in the head and neck, pelvic area and in the extremities. In this series of patients there does not seem to be any statistical difference in survival rates according to the tumor site but survival

TABLE 1. *Survival Related to Stage of Disease at Diagnosis*

	Prior to 1967		Since 1967	
	Number	Per cent Survivors	Number	Per cent Survivors
Stage I	13	30	23	86
Stage II	9	0	12	58
Stage III	7	0	3	0

TABLE 2. *Cell Types*

	Prior to 1967		Since 1967	
	Number	Per cent Survivors	Number	Per cent Survivors
Alveolar	5	60	5	60
Embryonal	14	0	24	75
Pleomorphic	10	10	9	66

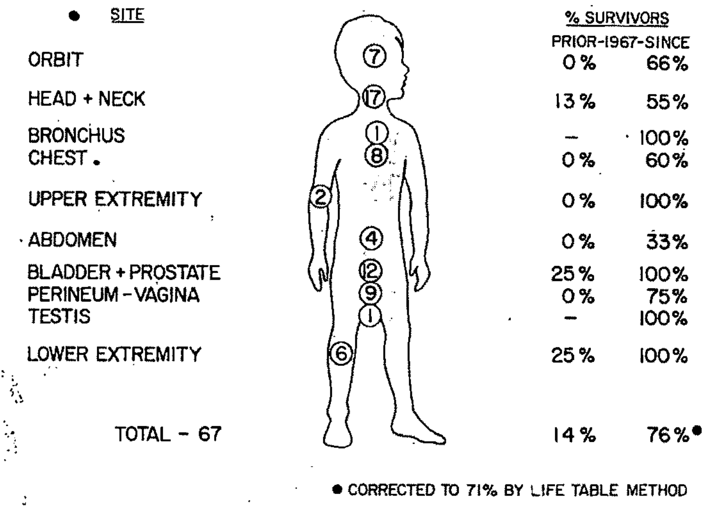


FIG. 2. Distribution of the tumor site as found in this series of patients.

is more closely related to stage of the disease at the time of diagnosis. Tumors occurring in the abdomen have a poor prognosis presumably due to later diagnosis. Since the adoption of the 1967 protocol program, there has been a 100% survival rate in tumors occurring in the extremities, bladder and prostate areas, testis and bronchus.

Type of Surgery

The type of operation performed was determined by the attending surgeon in each case. Most of these children had more than one procedure. Prior to 1967, operation was considered to be the only therapy that resulted in survivors and therefore surgical treatment was either very radical (including amputation) or consisted of biopsy only for Stage III disease. Since the adoption of the protocol in 1967, it became very obvious that reasonable operation, including complete excision of the tumor as possible, resulted in as good a survival rate as radical operation used with prophylactic chemotherapy and radiation therapy. The standard surgical procedure used has been extensive local resection with an attempt to conserve as much normal tissue as possible. No amputations have been performed for extremity lesions since 1967. For pelvic lesions, anterior exenteration with diverting ilioconduit cutaneous ureterostomies have been used for most of the tumors of the bladder and prostate. We have not performed prophylactic pelvic inguinal or periaortic lymphadenectomies. Head and neck lesions have in general been treated by radical neck dissection only if involved nodes were present. From the analysis of our material in Table 3, it is obvious that good survival rates can be achieved if there is adequate removal of all possible local tumor mass. Surprisingly, *biopsy alone* has provided a 33% survival rate in the series if the other adjuvants were used. Repeated local excision of recurrent tumors has been part of the therapy and is performed as often as needed to control the local tumor mass.

Summary of Therapy

Prior to 1967 and during the period of haphazard therapeutic regimen, four patients underwent operation alone and only one has survived. This boy is the longest survivor in this series and is alive 16 years after radical cystoprostatectomy performed in 1957 by Dr. J. P. Smith.[1] Three patients underwent operation with some palliative chemotherapy and none survive. Three patients underwent operation and radiation therapy and only one still survives. Nineteen patients underwent operation, radiation therapy and chemotherapy but not all were treated with prophylactic or repeated courses of chemotherapy. Two of these nineteen youngsters have survived.

Since the adoption of the protocol therapy program in 1967, of 38 patients only 32 underwent the full course of protocol therapy. Protocol therapy at The Columbus Children's Hospital has consisted of (1) complete removal of the tumor if possible with as much maintenance of normal anatomy as possible with re-resection if indicated at a later date; (2) radiation therapy with a corrected-for-age tumor dose of 2500 to 4000 rads to the primary site and known metastatic sites if present; (3) prophylactic cyclic therapy of actinomycin D and vincristine sulfate initiated in the immediate postoperative period. Seventy-five milligrams per kilogram of actinomycin D is given per course divided into five daily doses. This is followed by a 2-week drug-free period followed by 0.05 mg./Kg. dose of vincristine given at weekly intervals for 6 weeks. This 9-week schedule is then repeated for a 1-year period. Recently cyclophosphamide, as recommended by Children's Cancer Study Group A, has been added to this therapy. Of the 31 fully treated children, 87% survive, four were known to have disease at the time of this review (Table 4).

Discussion

Prognosis and the therapy of childhood rhabdomyosarcoma has been grim in the very recent past.[8] Sixty-

TABLE 3. *Type of Surgery*

	Prior to 1967		Since 1967	
	Number	Per cent Survivors	Number	Per cent Survivors
Biopsy Only	10	0	9	33
Incomplete Excision	6	0	7	86
Complete excision	2	100	15	80
Radical Excision	11	18	7	86
Repeat Local Excision	11	9	3	100
Metastatic Resection	3	33	3	33

TABLE 4. *Therapeutic Regimen*

	Surgery	Surgery and Chemo-therapy	Surgery and Radiation	Surgery, Radiation and Cyclic Chemo-therapy
Prior to 1967				
Number	4	3	3	19
Percent Survivors	25%	0%	33%	10%*
Since 1967				
Number	1	2	4	31†
Percent Survivors	100%	0%	25%	87%

* Not all prophylactic chemotherapy.
† Four patients with disease alive.

four cases of rhabdomyosarcoma in children from multiple institutions were reviewed in 1965 by the Children's Cancer Study Group A. There were only five survivors (7.8%) in this series of patients and all had been treated by *complete surgical removal of the primary tumor.* In 74% of these patients, metastatic disease developed during the first 6 months following operation, and in 83% by 1 year.[3] Therapy for this tumor had usually consisted of radical surgery alone and adjuvant radiation and chemotherapy has been reserved for recurrent or metastatic disease. It was obvious that treatment must be initiated prior to the development of metastatic disease and since radiation therapy had been used with little constant success, prophylactic chemotherapy seemed to be the next step. It was rapidly becoming clearer with each passing month of protocol therapy that this embryonal type of sarcoma will respond to combined types of therapy as does the nephroblastoma or Wilms' tumor.

Tumors of striated muscles were first described by C. O. Weber in 1854. Most of these tumors were treated by surgical means but in 1950 Stobbe and Dargeon[11] reported some rhabdomyosarcomas are relatively radiosensitive.[11] In 1952, Pack[9] reported rhabdomyosarcoma in an extremity that had been cured by surgical excision and radiation therapy without amputation. D'Angio, Farber and Maddock[2] in 1959 first observed the favorable synergistic effect of actinomycin D and radiation in the laboratory and applied this to the clinical management of neuroblastoma, nephroblastoma and rhabdomyosarcoma. Pinkel and Pickren[10] in 1961 suggested that a combined program of operation, radiation therapy and chemotherapy should be used for the treatment of rhabdomyosarcoma. In the same year Goodwin[5] successfully treated a boy with prostatic rhabdomyosarcoma with multiple modalities including some radiation therapy, chemotherapy and radical surgery. In 1965 prophylactic and repeated courses of chemotherapy were added to the management of rhabdomyosarcoma previously treated by operation and radiation. It quickly became obvious to us that the rate of survival was much better in the protocol-treated patients and this might well be related to the absence of pulmonary and distal metastases that commonly were seen in these patients and were usually present at the time of death in patients with rhabdomyosarcoma. Since the adoption of this protocol therapy, 38 patients have been treated for rhabdomyosarcoma. Only 11% (four of 38) have died during the first year of therapy and 76% (29 of 38) are alive at the end of 5 years, corrected to 71% survival by the actuarial life table method (Fig. 3).

This type of therapy used in the extremely young age group is producing survivors for the first time in this institution. Similarly, the site of the tumor seems to have little relationship to survival since the rate of survival has improved regardless of location. By contrast, the Stage I tumor seems to have the best prognosis and an 86% rate of survival has been achieved by use of the protocol therapy. Stage II disease, in addition to some regional lymph node involvement can result in better prognoses as indicated by the 58% survivorship with use of the protocol therapy in this series of patients. Stage III disease is still grim and the survival rate is very poor. Cell types seem to have little relationship as to survivorship if the protocol therapy is used.

Reasonable excisional surgery seems to remain the best method of initiating therapy of rhabdomyosarcoma; however, this may shortly change as several authors have initiated treatment with radiation, chemotherapy and follow-up operation with short-term success and less destructive surgical treatment.[4] By reasonable operation, we imply removal of as much tumor as possible with maximum conservation of normal anatomy, if feasible.

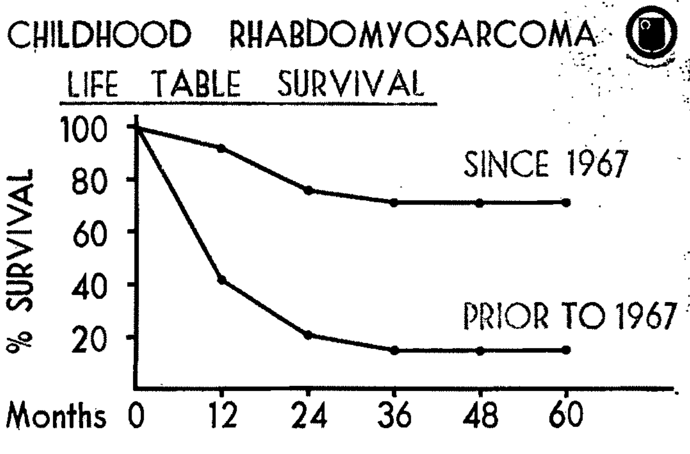


FIG. 3. Life table survival curves for this series of patients. The upper curve represents the group of patients treated by reasonable operation, radiation therapy and prophylactic, cyclic chemotherapy.

No amputations have been required with use of protocol therapy and we have been able to maintain a reasonable appearance of external genitalia in the management of the bladder, prostate and perineal rhabdomyosarcomas. One should remove as much gross tumor as possible at the primary procedure but it is obvious after review of our material that even though complete excision is expected after a radical surgical procedure, residual tumor was still present in the line of resection. This does not seem to be an important factor in survival if adjuvant therapy is used following surgical therapy. It would seem to us that once the tumor mass is removed and radiation therapy and chemotherapy are instituted, the combination of this therapy and the body's natural resource can manage any microcopic residual rhabdomyosarcoma or any disseminated tumor cells that might be present. We have noted a paucity of pulmonary metastases in our clinical material since the use of adjuvant therapy just as these pulmonary metastases have been controlled in the therapy of Wilms' tumors. Reasonable surgical treatment for childhood rhabdomyosarcoma without major mutilative surgery seems to be the answer as long as this operation is accompanied by radiation therapy and prophylactic, cyclic chemotherapy.

Summary

Childhood rhabdomyosarcoma has been treated in 67 children at The Columbus Children's Hospital in the period of time 1948 through 1972. Prior to 1967, 29 children with this tumor were treated by a variety of methods including conventional radical surgery. Fifty-eight per cent died within 1 year of diagnosis and only 14% survived for 5 years. In 1967 the planned protocol was instituted consisting of (1) complete removal of the tumor if possible and re-resection if indicated at a later date; (2) radiation therapy with a corrected-for-age tumor dose; (3) repeated cycles of actinomycin D and vincristine sulfate initiated in the immediate postoperative period. Since adoption of this mode of therapy 38 patients have entered the protocol therapy program with a diagnosis of rhabdomyosarcoma. Only 11% died within the first year of therapy and 71% are alive at the end of 5 years. Cell type seems unrelated to survival. *Reasonable* surgery seems as good as radical surgery as far as survival is concerned as long as adequate radiation therapy and the routine administration of multiple cyclic chemotherapeutic agents are used.

References

1. Bailey, W. C., Holaday, W. J., Kontras, S. B. and Clatworthy, H. W., Jr.: Rhabdomyosarcoma in Childhood: A Review of 14 Cases. Arch. Surg., 82:943, 1961.
2. D'Angio, G. J., Farber, S. and Maddock, C. L.: Potentiation of X-ray Effects by Actinomycin D. Radiology, 73:175, 1959.
3. Heyn, R. M., Holland, R., Newton, W. A., Jr. Tefft, M., Breslow, N. and Hartmann, J.: The Role of Combined Chemotherapy in the Treatment of Rhabdomyosarcoma in Children. For Children's Cancer Study Group A. (In Press.)
4. Ehrlich, F. E., Haas, J. E. and Kiesewetter, W. B.: Rhabdomyosarcoma in Infants and Children: Factors Affecting Long-term Survival. J. Pediat. Surg., 6:571, 1971.
5. Goodwin, W. E., Mims, M. M. and Young, H. H., II: Rhabdomyosarcoma of the Prostate in a Child: First 5-year Survival. (Combined Treatment by Preoperative, Local Irradiation; Actinomycin D; Intra-arterial Nitrogen Mustard and Hypothermia; Radical Surgery and Ureterosigmoidostomy) Trans. Am. Assoc. Genitourin. Surg., 59:186, 1967.
6. Grosfeld, J. L., Clatworthy, H. W., Jr. and Newton, W. A., Jr.: Combined Therapy in Childhood Rhabdomyosarcoma: An Analysis of 42 Cases. J. Pediat. Surg. 4:637, 1969.
7. Horn, R. C. and Enterline, H. T.: Rhabdomyosarcoma: A Clinicopathological Study and Classification of 39 Cases. Cancer, 11:181, 1958.
8. Mahour, G. H., Soule, E. H., Mills, S. D. and Lynn, H. B.: Rhabdomyosarcoma in Infants and Children: A Clinicopathologic Study of 75 Cases. J. Pediat. Surg., 2:402, 1967.
9. Pack, G. T. and Eberhart, W. F.: Rhabdomyosarcoma of Skeletal Muscle—A Report of 100 Cases—1929–1949. Surgery, 32:1023, 1952.
10. Pinkel, D. and Pickren, J.: Rhabdomyosarcoma in Children. JAMA, 175:293, 1961.
11. Stobbe, G. D. and Dargeon, W. H.: Embryonal Rhabdomyosarcoma of the Head and Neck in Children and Adolescents. Cancer, pp. 826–836, 1950.

Discussion

Dr. Willard E. Goodwin (Los Angeles): The authors are to be complimented on their excellent results. I rise to speak about urinary diversion. "Reasonable surgery," as we have heard in this excellent paper, advocates not being too radical; however, when the prostate or urinary bladder is involved with rhabdomyosarcoma, the surgery must be radical removal. Then urinary diversion has to be established.

I wish to speak in favor of *ureterosigmoidostomy* for urinary diversion in children, instead of ureteroileocutaneous diversion, because I think that this type of diversion improves the quality of the patient's life.

This slide illustrates an intravenous urogram before ureterosigmoidostomy in a young girl with a neurological bladder. Here is the excretory urogram 7 years later, nearly perfectly normal, and when, as in this slide, you see the patient herself, you can observe why a beautiful young girl, such as this, would prefer not to have an external urinary collecting device.

And here is a rhabdomyosarcoma of the prostate (I believe that it is the first 10-year cure of this dread disease). (Rhabdomyosarcoma of the Prostate in a Child: the First Five-Year Survival. J. Urol., 99:651, 1968). The patient had radical excision of the prostate seminal vesicles, bladder and bulbous urethra. He also received Actinomycin and radiation as advocated in this excellent paper. The urinary diversion was handled by ureterosigmoidostomy. As you can see in these slides of him in his active teen-age life, he is a healthy, active young man who swims, water skiis, and rides his motorcycle without the necessity of wearing an external urinary collecting device.

Dr. Joseph E. Murray (Boston): I wish to confirm this report of curability of rhabdomyosarcoma in children and cite our experience at the Children's Hospital Medical Center in Boston over the past 20 years.

I have two slides to show. The first was shown last fall before the American College of Surgeons and analyzes head and neck rhabdomyosarcoma. Notice there is a difference in curability depending on the anatomical site of the primary tumor.

The next slide shows that prior to 1957, the time we devised a radical cranio-orbital resection for recurrent rhabdomyosarcoma, we had no cures. These patients were dying without distant metastases but with massive locally recurrent disease.

Since that time, when we have added chemotherapy and radiation therapy to our radical surgery, we have six patients living and have lost only one. All survivors are between 5 and 12 years following treatment and are leading normal lives.

The main point to stress is that rhabdomyosarcoma, especially in children, is curable and currently deserves the maximum of all three modalities of treatment, namely: adequate surgery, chemotherapy, and irradiation therapy.

Dr. Norman Jaffe, Dr. Robert Filler, the late Dr. Sidney Farber, and I reported our results before the New England Surgical Society ("Rhabdomyosarcoma in Children. Improved Outlook with a Multidisciplinary Approach," *American Journal of Surgery* 125:482, 1973). The figure is about the same as reported by Dr. Kilman—approximately 75% total survival using a combination of the three modalities.

I cannot help but needle the authors about the term, "reasonable" surgery. I would presume that all surgical treatment is reasonable. If the authors wish to avoid the term "radical," it is their prerogative, but I would hope that all surgical treatment is adequate, thorough, and complete. Nor can I subscribe to the authors thesis that multiple local excisions is an acceptable way of handling any tumor. One surgical resection should be sufficient, and it should be adequate and thorough. It should encompass the local tumor, and in the current state of knowledge, it should be performed in conjunction with complete chemotherapy and irradiation therapy as indicated for the specific tumor.

Dr. Alexander H. Bill (Seattle): I have enjoyed this paper and it points out what is now known about this tumor. I should like to add one or two things to this: First of all, embryonal rhabdomyosarcoma which we are all taught was striated muscle possibly is not. It frequently arises in the genitourinary tract, male or female, and frequently in the pterygoid fossa. These are three places in which one finds very little striated muscle.

The second point I would like to discuss is the use of the drugs. This is the second tumor which has really responded to these adjuvants, the first being Wilms' tumor, the treatment for which was developed by the late Dr. Sidney Faber. This type of drug therapy has been more or less pragmatic. Why it works I think people really do not know. It is not harmful to the children. They maintain their well-being while on the drugs, and it has proved useful when it is used in addition to surgery and irradiation.

There is a message there somewhere, and if we could learn how these work and then how to test them by the use of tissue culture sensitivity tests, their usefulness might be extended to other tumors.

Dr. James W. Kilman (Closing): Dr. Goodwin's work is known to us and he probably has the longest-term survivor as far as post-surgical therapy for rhabdomyosarcoma.

Dr. Murray's data supports our work as to the survival rate therapy and we appreciate his remarks.

We have meant by multiple procedure that biopsy was usually the first procedure that was done and this was followed by extensive excision as was felt indicated.

It is interesting to note that in review of some of this material that practically 80 to 90% of the resection lines of the tumors that have been resected show microscopic tumor and a good number obviously of these patients are long-term cures even with tumor in the line of resection at the time of the reasonable or radical surgical procedure.

It is interesting that in our series we have had the one case of a tumor of the bronchus. This has been reported eight or nine other times in the literature and obviously the bronchus does not contain striated muscle but only smooth muscle. These rhabdomyosarcomas can originate in other places where there is obviously no striated muscle located.

The therapy we feel is effective during the time of originating or circulating tumor cells and that perhaps the chemotherapy does prevent the metastatic spread by this initial and cyclic chemotherapy immediately following surgery.

Immunotherapy in Patients with Melanoma

H. F. SEIGER, W. W. SHINGLETON, R. S. METZGAR, C. E. BUCKLEY, III.,
P. M. BERGOC

From the Department of Surgery, Immunology and Medicine Duke University Medical Center, Durham, North Carolina

Throughout medical history biologists have noted a wide variation in the response of patients to the neoplastic process. Spontaneous tumor regression, complete or partial, has been described by numerous authors.[9,20] Regression with severe infection stimulated a popular belief that host immune response to the infection was also responsible for tumor regression. This was the background that led Coley[7] at the turn of the century to evaluate bacterial toxins in patients with malignant tumors and he extended his observations to include a more successful response if the toxin was introduced directly into the tumor site. Immunoprophylaxis for the prevention of infectious diseases gained an important role in medical science throughout the first half of this century. Gross[12] applied these technics in a rodent system to demonstrate that animals could be protected from tumor-take by immunization against particular methylcholanthrene tumors. Old[25] added data supporting the immune response by demonstrating that BCG immunization of the host decreased tumor-take in the rodent.

Eradication or arrest of an established tumor in both animal models and in man has been unsuccessful. For immunotherapy to be effective certain basic circumstances should be evident. First, tumor specific or tumor associated antigens should be present on the surface of the tumor cells. Second, the immunologic response to these antigens should be adequate and this includes both the cellular and humoral response. Third, there should be absence of blocking or enhancing antibody present in the patient's serum. Animal experiments indicate that individually specific tumor associated antigens play the dominant role in chemically induced tumors,[28] while common tumor associated antigens characterize tumors of a known viral etiology.[33] Immunofluorescent studies as well as immunization experiments in animals strongly suggest that the tumor antigens are transplantation type antigens.[8,18] Host immune mechanisms can inhibit growth of neoplasms, and this tumor immunity has been well documented in experimental animal model systems. Zbar and Tanaka[35] have demonstrated tumor immunity following intratumor inoculation of living *Mycobacterium bovis*. Rapp[29] has induced regression of an established tumor in guinea pigs by intratumor injection of specifically sensitized lymphocytes. Mathé[22] and Powles[27] have noted marked prolongation of remission in leukemia patients utilizing serial immunizations with irradiated leukemia cells and BCG. Both Morton[24] and Seigler[31] have observed local, and in some cases, systemic immunity in patients with melanoma treated with intratumor injections of BCG. Inoculation of patients with specific transfer factor has gained increasing attention and seems to specifically increase cell-mediated immunity.

In vitro monitoring of multiple aspects of the immune system in patients has been made possible by advancements in sophisticated methodology. This report includes study of multiple attributes of the immune system before and during nonspecific and specific immunotherapy in 142 patients with metastatic melanoma. Sequential monitoring has allowed us to assess changes induced by immunotherapy and the correlations with the clinical course.

Methods

All patients selected for immunotherapy had previously undergone combinations of surgical treatment, irradiation, limb perfusion, and chemotherapy and subsequently developed recurrent disease. Informed consent was obtained prior to initiation of experimental therapy.

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25–27, 1973.

Supported in part by Clinical Cancer Center Grant No. CA 11265 at the Duke University Medical Center, Durham, North Carolina and Veterans Administration Surgical Research Funds, Durham, North Carolina.

TABLE 1. *Antigen Panel for Evaluation of Immune Competence*

Antigens	Dilutions	Antigens	Dilution
Alpha streptococcus	10^{-4}	PPD	0.002 mg.
H. influenza	10^{-4}	Blastomycin	10^{-3}
N. catarrhalis	10^{-4}	Histoplasmin	10^{-3}
S. epidermidis	10^{-4}	Coccidiodin	10^{-3}
Proteus mirabilis	10^{-4}	Oidiomycin	10^{-3}
Pseudomonas	10^{-4}	Trichophyton	10^{-3}
S. aureus	10^{-4}	Alternaria	2×10^{-3}
Enterobacter	10^{-4}	Aspergillus	2×10^{-3}
E. coli	10^{-4}	Hormodendrum	2×10^{-3}
Pneumococcus	10^{-4}	Rhizopus	2×10^{-3}
Enterococcus	10^{-4}	Mumps	Undiluted
Mixed respiratory	10^{-1}		

The Immunotherapy Plan. The predicted course of immunotherapy is divided into four stages; two initial nonspecific stages and two specific stages.

Stage I. In the first stage, immunologic evaluation is followed by BCG sensitization. This step is designed to activate the immune system toward a specific but indifferent delayed allergen.

Stage II. In this stage, intratumor injection of cutaneous or subcutaneous metastases with BCG is accomplished. This stage is designed to recruit a delayed hypersensitivity response within the tumor nodule.

Stage III. An American Celltrifuge separator is used to obtain approximately 5×10^9 lymphocytes from the patient; the autologous lymphocytes are specifically activated *in vitro* with an equal number of irradiated neuraminidase treated tumor cells. Following a 72-hour incubation period the cells are readministered to the patient subcutaneously or intratumor. This stage is designed to test the effectiveness of an adoptive transfer of cell mediated immunity.

Stage IV. The patient is challenged with a subcutaneous inoculum of irradiated neuraminidase treated autochthonous tumor cells plus BCG. This stage is designed to test the capacity of active immunization to augment tumor immunity. Each stage is spaced from 6 to 8 weeks apart; each treatment is preceded by a complete re-evaluation of the previously measured immunological parameters designed to sequentially document changes in cell-mediated and humoral immunity.

Studies of Humoral Immunity. Serum concentrations of IgG, IgA, and IgM were measured by single radial diffusion methods previously reported.[5] Serologic studies for tumor specific antibodies were accomplished by complement fixation, mixed agglutination and cytotoxicity.[23,10]

Studies of Cell-mediated Immunity. Cutaneous hypersensitivity was evaluated with a panel of antigens having defined reactions in 138 patient controls (Table 1). The response to an intradermal injection of 0.05 ml. of each antigen was measured and recorded as previously reported.[31] *In vitro* lymphocyte activation was measured by a modification of the semi-micro method of Bach.[2] The stimulation indices were calculated and recorded as previously reported.[31] The lysis of tumor cells *in vitro* by patient lymphocytes was assayed by the method of Jagarlamoody and associates[17] with radiolabeled melanoma tissue culture monolayers. Blocking factors in the patient's serums were assayed by a modification of this technic.[17]

Blood Cell Separation. Leukophoresis was accomplished with a continuous flow blood cell separator (Celltrifuge, American Instruments). The bowl flow rate was 40 cc. per minute, and the roter speed was 1,100 rpm. A cell concentrate containing an average of 5×10^9 lymphocytes was collected over a 4 to 5-hour period in two 300 cc. bags containing 2 cc. of heparin and 15 cc. of ACA-A; maximum granulocyte and monocyte contamination was 25 to 30%.

Results

One hundred and forty-two patients with metastatic melanoma have been treated by the described immunotherapy regimen.

Serum immunoglobulin levels did not change during immunotherapy. Figure 1 presents observations at Stages I-IV of treatment. Measurements prior to BCG therapy

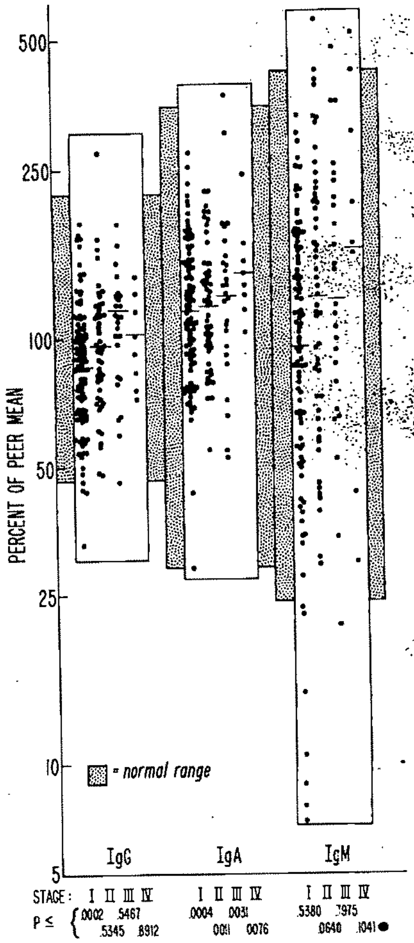


FIG. 1. Serum immunoglobulin levels in patients with malignant melanoma.

TABLE 2. *Serologic Evaluation for Tumor Specific Antibody in First Seventy Patients Studied*

Number of Patients	Serologic Technics	Positive Reactions
70	Mixed Agglutination	17
70	Complement Fixation	20
70	Cytotoxicity	30

revealed a low geometric mean serum IgG ($p = 0.0002$), elevated IgA ($p = 0.0004$) with a wide distribution of IgM levels without significant departure of the geometric mean from that of age, race and sex matched peers. Patients completing all stages of BCG therapy exhibited a trend toward increased geometric mean IgG and IgM levels; but differences from controls were small and not statistically significant. Serum IgA levels also exhibited this upward trend and geometric mean levels remained greater than levels in controls. This apparent trend toward elevated serum immunoglobulin levels could represent a consequence of therapy or survival and selection of patients with elevated serum immunoglobulin levels. The hypothesis that levels changed with therapy was tested by comparing levels observed at Stages II, III and IV with levels observed prior to Stage I in each remaining patient. This provided a total of 54 comparisons. Serum levels of IgG ($p = 0.4049$), IgA ($p = 0.2364$) and IgM ($p = 0.9404$) did not change significantly during the course of therapy. This suggests that the apparent upward trend in serum immunoglobulin levels observed during treatment reflects selection of patients with relatively high serum immunoglobulin levels. This implies that patients with relatively low levels of IgA and IgG did not survive to enter subsequent stages of therapy.

Serologic evaluation for tumor specific antibody revealed a positive response in 31 of our first 70 patients studied (Table 2). Seventeen of 31 were positive by mixed agglutination, 30 of 31 by cytotoxicity and 20 of 31 by complement fixation. The sera became more reactive as the patients progressed through the stages of treatment; however, insufficient numbers do not allow a statistical evaluation at this time. Specificity studies revealed that all positive sera remained positive after absorption with HeLa, Hep, three normal skin fibroblast cell lines and pooled normal lymphocytes to remove all HL-A activity (Table 3). Only three of the 70 patients' sera tested reacted by direct testing with normal lymphocytes, HeLa, Hep, and three normal skin fibroblast cell lines. Obviously, additional direct testing and absorptions will be necessary to more firmly establish tumor specificity.

TABLE 3. *Serum Absorption Studies for Tumor Specificity*

Number of Sera Absorbed	Absorbed with	Serum Reaction After Absorption
31	HeLa	Positive
31	Hep	Positive
31	3 normal fibroblast lines	Positive
31	Pooled normal lymphocytes	Positive

An assessment of cutaneous hypersensitivity with the antigens listed in Table 1 exhibited generally decreased ability to generate inflammatory changes in skin necessary for characteristic expression of hypersensitivity reactions in this patient population. In the first 114 patients studied 48 or 42.1% were hyporesponsive at 48 hours to the delayed allergens and 4 or 3.5% were normal or near normal while 62 were completely unresponsive (Fig. 2). While hyporesponsiveness to the test antigens was clearly correlated with diffuse systemic disease, responsiveness could not clearly be correlated with regression of disease during the immunotherapy course. Among the first 98 patients studied, death or tumor regression did not halt sequential stages of therapy in 18 patients. Cutaneous hypersensitivity responses were followed through all four stages of treatment. Seven patients exhibited tumor regression or inactive disease on the basis of apparent freedom from metastatic tumor at the time of this report. These patients were categorized as having complete or partial remission. In 11 patients the tumor disease continued or they died following completion of therapy. These patients were categorized as having tumor regression. Figure 3 summarizes cutaneous hypersensitivity responses averaged over all antigens in these two groups of patients. Geometric mean cutaneous responses and the ±2 standard error of estimate range at each stage of therapy are presented for each group of patients. Similar averages of responses in patient controls are presented for comparison. An estimate of the significance of the departure of the responses observed in melanoma patients from responses in controls is presented at the top of Figure 3. Anaphylactic (0.25 hours) and the early Arthus (6.0 hours) hypersensitivity were increased. The 24-hour Arthus response and 72-hour delayed cutaneous responses did not differ significantly from controls. Delayed hypersensitivity at 48 hours was significantly decreased. This suggests that increased anaphylactic and early Arthus hypersensitivity and decreased delayed hypersensitivity was characteristic of this unique group of patients with metastatic melanoma.

Multivariate comparison of cutaneous hypersensitivity between patients with remission and progression of the tumor disease revealed highly significant differences ($p = 0.0064$). Univariate contrasts of measured responses which accounted for this difference consisted of increased anaphylactic hypersensitivity ($p = 0.0370$) and decreased delayed hypersensitivity at 48 ($p = 0.0036$) and 72 hours ($p = 0.0049$). Although multivariate analysis indicated therapy-related changes in cutaneous hypersensitivity in patients undergoing remission were not significant ($p = 0.0985$), univariate contrasts suggested

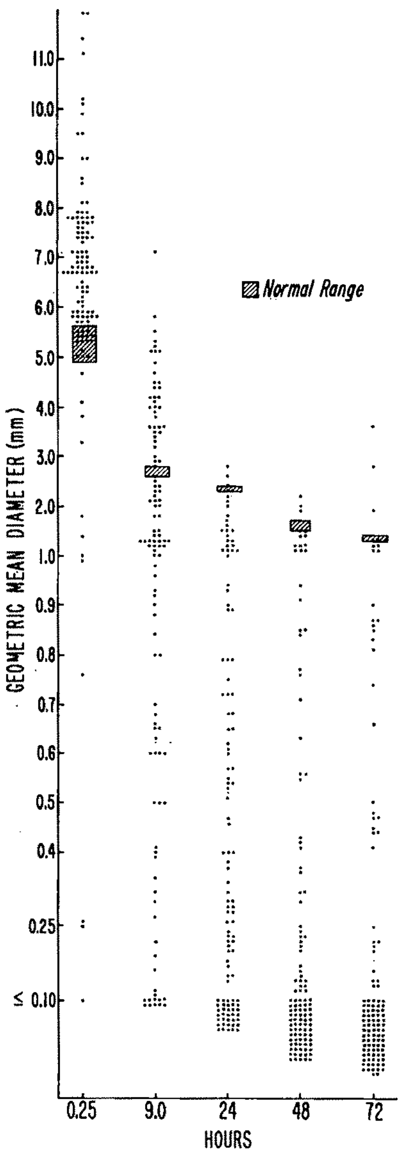


FIG. 2. Cutaneous hypersensitivity reactions in patients with malignant melanoma. Each point represents the geometric mean cutaneous response to the same 23 antigens in a patient. The boxes enclose the 95% confidence interval in control patients at each time point. Reactions ≤ 0.1 mm were not measurable. The probability of no response to all 23 antigens at 72 hours (reactions ≤ 0.1 mm) $>1:75,000$.

possible differences in anaphylactic ($p = 0.0434$) and early Arthus hypersensitivity ($p = 0.0325$). Among patients with tumor progression, multivariate evaluation of the effects of therapy revealed no significant differences ($p = 0.3006$); univariate comparisons were also not significant. The first order interaction of differences in tumor disease and the effect of therapy were not significant ($p = 0.9515$). This suggested averaged measures of cutaneous hypersensitivity detected differences related to the severity of tumor disease, but not the effects of therapy.

In contrast, differences related to therapy and the severity of disease were detected with the response to specific antigens. Multivariate comparison of the responses to PPD, oidiomycin and mumps antigens between patients with remission and progression of tumor disease revealed no significant differences ($p = 0.2185$). Responses to specific antigens were averaged over all patients at each time of observation and stage of therapy.

Multivirate comparisons of the responses contributed to the averages presented at each stage of therapy in Table 4 suggested highly significant changes could be detected with measures of hypersensitivity to PPD ($p \leq 0.0001$), oidiomycin ($p \leq 0.0001$) and mumps ($p \leq 0.0019$) antigens. The probabilities presented in Table 4 reflect univariate estimates of the significance of trends observed at each time of measurement. Cutaneous hypersensitivity to PPD increased at all times of observation except for the 0.25-hour anaphylactic response. The maximum change following BCG therapy was detected with the 24-hour Arthus response—a 6-fold change was induced during the course of treatment. Cutaneous hypersensitivity to oidiomycin also increased, but significant trends were restricted to measures of anaphylactic and Arthus hypersensitivity. Delayed cutaneous hypersensitivity increased transiently and then decreased—the overall trend was not significant. Anaphylactic hypersensitivity to mumps antigen increased significantly. In contrast, delayed cutaneous hypersensitivity to mumps virus antigen decreased; changes in Arthus hypersensi-

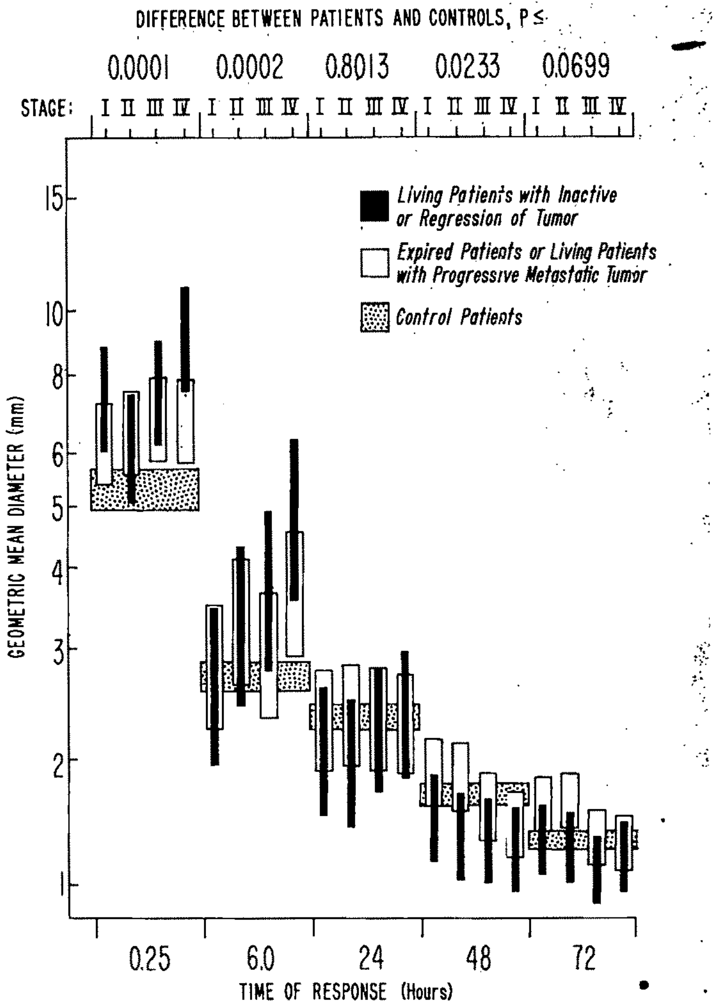


FIG. 3. Difference between patients and controls.

TABLE 4. *Cutaneous Hypersensitivity Responses To PPD and Two Control Antigens in 18 BCG Treated Melanoma Patients*

			Diameter of Geometric Mean Response, in millimeters at each time of measurement				
Antigen	Stage	Hours	0.25	6.0	24	48	72
PPD	1		6.7	2.8	2.2	2.1	2.3
	2		6.1	5.6	8.7	7.8	7.3
	3		6.9	9.4	13.0	8.9	7.5
	4		6.4	12.9	13.4	9.3	7.6
		$p \leq$	0.6961	0.0001	0.0001	0.0001	0.0002
Oidiomycin	1		8.2	2.7	6.6	7.8	7.2
	2		9.4	7.2	13.8	10.1	7.9
	3		9.1	9.4	11.9	9.6	5.1
	4		12.5	14.1	19.7	7.5	3.8
		$p \leq$	0.0052	0.0001	0.0073	0.6712	0.1112
Mumps	1		8.5	4.9	7.3	7.6	5.3
	2		8.1	6.5	5.3	3.7	3.6
	3		10.5	7.1	5.6	3.2	2.1
	4		11.9	7.9	4.7	2.0	1.8
		$p \leq$	0.0217	0.2674	0.6228	0.0015	0.0018

tivity were not significant. These comparisons suggest the averaged comparisons presented in Figure 3 may obscure opposing trends in specific cutaneous responsiveness. Although augmented responsiveness to PPD during BCG therapy was not unexpected, the more restricted changes in responsiveness to antigens such as oidiomycin and mumps were not anticipated. The decrement in responsiveness to mumps virus antigen suggests nonspecific augmentation of delayed cutaneous hypersensitivity was not a general consequence of BCG immunotherapy.

Evaluation for lymphocyte responsiveness *in vitro* was completed prior to initiation of therapy, following Stage II of therapy, and at completion of Stage IV of treatment. The stimulating antigens included phytohemagglutinin, unrelated lymphocytes that had been mitomycin treated, x-irradiated neuraminidase treated autochthonous tumor cells, PPD, pokeweed mitogen, x-irradiated unrelated skin fibroblasts, and mitomycin treated autologous lymphocytes served as a control. The general observation in this patient group prior to initiation of therapy revealed normal response to phytohemagglutinin alone. It is of interest that the regimen reversed the unresponsiveness of patient lymphocytes in those that became skin test positive and developed cell-mediated immunity. The results in the first 26 patients completing therapy are depicted in Table 5. The normal or near normal response to PHA reflects adequate T lymphocyte activity and the response to pokeweed mitogen reflects adequate B cell activity. Cell-mediated immunity was studied *in vitro* utilizing radiolabeled tissue culture monolayers. Patient lymphocytes were added to the labeled tumor monolayer and if cellular immunity was present cytolysis occurred and isotope was released. Isotope counting of the remaining monolayer reflected the degree of lysis of the target cell. The control utilized normal skin fibroblasts. Cellular immunity evaluation in the first 62 patients completing the immunotherapy regimen revealed that 43 of 62 were positive. The range of the per cent of lysis of the tumor monolayer was 20 to 90% and the mean percentage was 60.5%. All 19 patients without cellular immunity demonstrated diffuse disease which progressed to death of the patient (Table 6). With only few exceptions, the patients that developed cellular immunity also were converted to responsiveness *in vivo* to at least one of the delayed skin allergens. Serum blocking factor was evaluated by a modification of the technic in which the patient's serum is added instead of normal human sera and if blocking factors are present decreased or no lysis of the monolayer will be noted. Utilizing this technic it was noted that in the 62 patients thus tested 21 of 62 were positive for serum blocking factors (Table 7). The range of the degree of blocking included 20 to 80% and the mean was 57.5%. The presence or absence of serum blocking factor, however, did not absolutely correlate with the clinical course. Blocking factor was not present in 20 patients that had progression of disease to death.

TABLE 5. *Stimulation Indices in Twenty-Six Patients Completing Immunotherapy*

Stimulating Antigen†	Means Stimulation Index*
PHA (20 μL of 1:10 dilution)	59.3
Unrelated lymphocytes‡	14.0
Melanoma cells§	11.0
PPD (50 μL/2ml.)	3.6
BCG (100 μL/2 ml.)	2.5
Pokeweed (10 μL of 1:5 dilution)	19.3
Unrelated fibroblasts§	2.2
Autologous lymphocytes‡	1.0

* The degree of stimulation in each test was expressed as a ratio between the mixture and the appropriate control, called the stimulation index.

† PHA, phytohemagglutinin: PPD, purified protein derivative; BCG, bacillus Calmette-Guerin.

‡ Mitomycin treated.

§ 5000 rads irradiation.

At the present time an overall evaluation in this patient series reveals that 34% of the patients have died of causes secondary to the melanoma process, 43% continued to have the disease and 23% have had complete regressions and remain free of disease. The study has been in progress for approximately 3½ years and some patients have remained well for the entire period. This follow-up period is obviously too short to firmly assess the immunotherapy regimen or to predict the overall effectiveness of this mode of treatment. The patient category that has benefited from this regimen includes only those patients in whom the metastatic disease has been confined to the skin, subcutaneous tissue and lymph nodes. If the disease has progressed to involve the parenchyma, skeleton or central nervous system, the responses have been very transient and are of no clinical significance.

Discussion

It has been difficult to determine whether tumor associated antigens are tissue specific rather than tumor specific. There is evidence that common tumor associated antigens, detected in human alimentary tract carcinomas, are of an embryonic nature and thus the result of de-repression or "unmasking" of normal fetal antigens.[11] Mounting data indicate that the common tumor associated antigens are caused by viruses that have either induced the tumor or become secondarily involved with them. The biochemical nature of tumor specific or tumor associated antigens and the host immune response to them continues to be poorly understood. Immunotherapy is based on the principle that immunity can be augmented toward a tumor specific antigen by the adjuvant activity of a nonspecific agent or by specific immunization.

Tumor cell destruction is believed to result primarily from heightened cell mediated immunity, however, the exact role of humoral immunity remains unclear. It has been reported that lymphocyte and plasma cell infiltration into tumors often indicates a favorable prognosis.[4] The Hellstroms[13] described a colony inhibition test that demonstrated lymphocyte-mediated inhibition of neoplastic cells. Hellstrom and associates,[15] Jagarlamoody and associates[17] and Cohen[6] have all demonstrated cellular immunity *in vitro* utilizing different technics reflecting cell-mediated cytolysis. The degree of tumor cell destruction appears to be the same in patients who were studied with either widespread disease or from whom tumors had been successfully removed. Varying success has been reported from studies utilizing cutaneous delayed hypersensitivity reactions elicited by soluble antigen extracts prepared from tumors. Impaired lymphocyte reactivity in culture in our patient population is of great interest. The observation that lymphocyte activity could be recovered by the nonspecific and specific stimulation of the host suggests that the host-immune response is not irrevocably lost. The degree of stimulation by phytohemagglutinin and pokeweed mitogen reflects normal T and B cell responses. The stimulation noted by the irradiated neuraminidase treated autochthonous tumor cells suggests that the stimulation is secondary to the tumor neoantigen. This is a very important point if indeed adoptive transfer of specifically sensitized cells is to prove beneficial in patients with established neoplasms.

The observation that patients with intact delayed hypersensitivity have a better prognosis with their neoplastic process than anergic or hyporesponsive patients indicates the importance of the host-immune mechanism.[8] Patients who are on immunosuppression will accept a tumor allograft.[36] Penn and coworkers have reported an incidence of 6% of spontaneous neoplasms in 184 kidney transplant recipients.[26] Recent kidney registry data indicate that approximately one-half of the neoplasms are of epithelial origin and the other half originate in the reticulo-endothelial system. Immunoprophylaxis from malignancy as reported recently by Rosenthal[30] points to the need for investigation in the area of immunotherapy. Nonspecific stimulation of the immune system by an agent such as BCG can stimulate local host immunity;[24,31] it does not, however, predictably produce systemic immunity.[31] Adoptive transfer of tumor immunity has been demonstrated in the rodent,[29] and attempts to elicit specific cellular immunity in tumor regression in melanoma by administering specifically sensitized autologous lymphocytes has been suggested.[31] Simmons *et al.*[32] have reported alteration of membrane antigens by neuraminidase treatment and this increased immunogenicity has efficiently provided specific regression of established chemically induced rodent tumors.

TABLE 6. *Cellular Immunity in 62 Melcnoma Patients*

Number of Patients	Cellular Immunity	Per cent
43	Positive	69
19	Negative	31

Range of Lysis — 20 to 90%
Mean = 60.5%

Humoral immunity has been observed in the sera of patients from whom localized melanomas have been surgically removed. These humoral antibodies have been proved to be cytotoxic in the presence of complement,[21] and they have been used to demonstrate a surface localized antigen in melanomas by immunofluorescent technics.[18]

The Hellstroms[13] have demonstrated that blocking serum factors are present in the sera of patients with wide-spread malignancies. These blocking factors are not generally present in the sera of patients that have undergone curative surgery.[13] Sjogren[34] has postulated that the serum blocking factor may be antigen-antibody complexes that interferes with lymphocyte reactivity thus allowing tumor growth. Sera from certain patients who have been rendered tumor free have demonstrated an *unblocking* effect.[14] Alexander and Currie[1] have noted that the serum inhibitor does not combine with the target tumor cell and they suggest that the active material is circulating tumor-specific antigen which in the *in vitro* assay competes with the tumor cell for the cytotoxic

TABLE 7. *Serum Blocking Factor in 62 Melanoma Patients*

Number of Patients	Blocking Factor	Per cent
21	Positive	34
41	Negative	66

Range of Blocking — 20 to 80%
Mean = 57.5%

lymphocytes. Baldwin[3] recently proposed that the blocking activity of tumor-bearing serum is associated with tumor-specific immune complexes. This is supported by the finding that post-excision serum, which contains cytotoxic antibody but no blocking activity, can be converted so as to produce blocking by the addition of a solubilized preparation of tumor-specific antigen.

Our present level of understanding of tumor immunity suggests that there is both a cellular and humoral-immune response directed against both common and specific tumor associated antigens. The concert of cellular events responsible for tumor destruction by cell-mediated cytolysis most probably includes T and B cell interactivity as well as an ever important macrophage response. The immunocompetent cell can be blocked at either the *killer* cell level or the target cell level. Blocking at the target cell level is most probably caused by antibody interaction with the tumor cell as well as interference by antigen-antibody complexes. The blocking of lymphocyte cytotoxicity is a complex event which is predominantly mediated by the presence of excess free tumor antigen in the system attaching to the cell-bound antibody. There may also be a contributing blocking effect by free antigen-antibody complexes which adhere to the immunocompetent cell-preventing cell-mediated cytolysis.

Summary

One hundred and forty-two patients with metastatic melanoma have been treated with a staged immunotherapy plan including two nonspecific stages and two specific stages. Immunologic and clinical responses were monitored in an effort to note correlations with the immunotherapy regimen. Clear immunoglobulin deficiency was not present in this patient population. Impaired delayed cutaneous hypersensitivity responses were, however, generally noted. Thirty-one of the first 70 patients completing the treatment gained tumor specific humoral immunity as detected by at least one serologic technic. The immunotherapy course proved consistent in producing cellular immunity in 43 of the first 62 patients completing treatment. In all 19 patients that remained negative for cell-mediated immunity, the disease progressed until death. Serum blocking factors were evaluated and 21 of the 62 patients were positive for substances in their sera that interfered with tumor inhibition *in vitro*. The follow-up periods include 3 to 39 months and 34% of the patients have died of causes secondary to the melanoma, 43% continue to survive but have detectable disease and 23% have been rendered free of disease for this time course.

References

1. Alexander, P. and Currie, G. A.: The Role of Circulating Tumor-Specific Antigens in the Tumor-Host Relationship. Immunological Aspects of Neoplasia. Evan M. Hersh and Max Schlamowitz, editors, In Press.
2. Bach, M. L., Salliday, S. and Stambuk, M.: Histocompatibility Matching: I. Detection of Disparity in the Mixed Leukocyte Culture Test: A More Rapid Assay. Histocompatibility Testing, 1970.
3. Baldwin, R. W., Price, M. R. and Robins, R. A.: Characterization of Serum Factors Blocking Lymphocyte Cytotoxicity for Tumor Cells. Immunological Aspects of Neoplasia. Evan M. Hersh and Max Schlamowitz editors, In Press.
4. Black, M. M. and Speer, F. D.: Sinus Histiocytes of Lymph Nodes in Cancer. Surg. Gynecol. Obstet, 106:163, 1958.
5. Buckley, III, C. E. and Dorsey, F. C.: Serum Immunoglobulin Levels Throughout the Lifespan of Healthy Man. Ann. Intern. Med., 75:673, 1971.
6. Cohen, A. M. and Ketcham, A. S.: A Technique for Demonstrating in vitro Cell-mediated Cytotoxicity Using I-125 Labelled Target Cells. J. Immunol., In Press.
7. Coley, W. B.: Some Clinical Evidence in Favor of the Extrinsic Origin of Cancer. Surg. Gynecol. Obstet., 59:353, 1925.
8. Eilber, F. R. and Morton, D. L.: Immunological Studies of Human Sarcomas. Additional Evidence Suggesting an Associated Sarcoma Virus. Cancer, 26:588, 1970.
9. Everson, T. C., and Cole, W. H.: Spontaneous Regression of Cancer. Philadelphia and London, Saunders Co., pp. 560, 1966.
10. Fernald, G. W. and Metzgar, R. S.: Detection of Alloantigens on Human and Chimpanzee Skin Fibroblasts in vitro Cytotoxicity and Colony Inhibition Tests. Transplantation, 12: 211, 1971.
11. Gold, P.: Circulating Antibodies Against Carcinoembryonic Antigens of the Human Digestive System. Cancer, 20:1663, 1967.
12. Gross, L.: Intradermal Immunization of C3H Mice Against a Sarcoma that Originated in an Animal of the Same Line. Cancer Res., 3:326, 1943.
13. Hellstrom, I., Hellstrom, K. E., Pierce, G. E., Yang, J. P. S.: Cellular and Humoral Immunity to Different Types of Human Neoplasms. Nature (London), 220:1352, 1968.
14. Hellstrom, I., Hellstrom, K. E., Sjogren, H. O., and Wainer, G. A.: Serum Factors in Tumor-Free Patients Cancelling the Blocking of Cell-Mediated Tumor Immunity. Int. J. Cancer, 8:185, 1971.
15. Hellstrom, K. E. and Hellstrom, I.: Immunological Enhancement as Studied by Cell Culture Techniques. Ann. Rev. Microbiol., 24:373, 1970.
16. Hellstrom, I., Sjogren, H. O., Warner, G. A., and Hellstrom, K. E.: Blocking of Cell-Mediated Tumor Immunity by Sera From Patients with Growing Neoplasms. Int. J. Cancer, 7:226, 1971.
17. Jagarlamoody, S. M., Aust, J. C., Tew, R. H. and McKhann, C. F.: In vitro Detection of Cytotoxic Cellular Immunity Against Tumor Specific Antigens by a Radioisotopic Technique. Proc. Natl. Acad. Sci., 68:1346, 1971.
18. Klein, E. and Sjogren, H.: Humoral and Cellular Factors in Homograft and Isograft Immunity Against Sarcoma Cells. Cancer Res., 20:452, 1960.
19. Klein, G.: Immunological Studies on a Human Tumor. Isr. J. Med. Sci., 7:111, 1971.
20. Koop, C. E., Kiesewetter, W. B. and Horn, R. C.: Neuroblastoma in Childhood, Surgery, 38:272, 1955.
21. Lewis, M. G., Ikonopisov, R. L., Nairn, R. C., Phillips, T. M., Fairley, G. H., Bodenham, D. C. and Alexander, P.: Tumor-Specific Antibodies in Human Malignant Melanoma and Their Relationship to the Extent of the Disease. Brit. Med. J., 3:547, 1969.
22. Mathe, G., Amiel, J. L., Schwarzenberg, L., Schneider, M., Cattan, A., Schalmberger, J. R., Hayat, M., and de Vassal, F.: Active Immunotherapy for Acute Lymphoblastic Leukemia. Lancet, 1:697, 1969.

23. Metzgar, R. S., Flanagan, J. F. and Zmijewski, C. M.: Detection of Tissue Antigens on Primary and Serial Heteroploid Cell Lines of Human Origin by Mixed Agglutination Technique. J. Immunol., **95**:494, 1965.

24. Morton, D. L., Eilber, F. R., Malmgren, F. A. and Wood, W. C.: Immunological Factors Which Influence Response to Immunotherapy in Malignant Melanoma. Surgery, **68**: 158, 1970.

25. Old, L. J., Benacerref, B., Clarke, D. A., Carswell, E. A., Stockert, E. Cancer Res., **21**:1281, 1961.

26. Penn, I., Halgrimson, C. G. and Starzl, T. E.: De Novo Malignant Tumors in Organ Transplantation. Transplant. Proc., **3**:773, 1970.

27. Powles, R.: Immunotherapy of Acute Myelogenous Leukemia in Man. J. Natl. Can. Inst., In Press.

28. Prehn, R. T., Main, J. M., Immunity to Methylcholanthrene-Induced Tumors. J. Natl. Canc. Inst., **18**:769, 1957.

29. Rapp, H. J.: Immunotherapy of a Guinea Pig Hepatoma. Natl. Canc. Inst. Clinical Investigations Branch, Symposium on Tumor Immunology, Atlanta, Ga., Nov. 1970.

30. Rosenthal, C., Crispen, R. G., Thorne, M. G., Piekarski, N., Raisys, N. and Rettig, P. G.: BCG Vaccination and Leukemia Mortality. JAMA, **222**:1543, 1972.

31. Seigler, H. F., Shingleton, W. W. Metzgar R. S., Buckley, C. E., III., Bergoc, P. M., Miller, D. S., Fetter, B. F. and Phaup, M. B.: Nonspecific and Specific Immunotherapy in Patients with Melanoma. Surgery, **72**:162, 1972.

32. Simmons, R. L. and Rios, A.: Combined Use of BCG and Neuraminidase in Experimental Tumor Immunotherapy. Surg. Forum, **22**:99, 1971.

33. Sjogren, H. O.: Transplantation Methods as a Tool for Detection of Tumor-Specific Antigens. Progr. Exp. Tumor Res., **6**:289, 1965.

34. Sjogren, H. O., Hellstrom, I., Bansal, S. C., Hellstrom, K. E.: Suggestive Evidence that the "Blocking Antibodies" of Tumor-Bearing Individuals May be Antigen-Antibody Complexes. Proc. Nat. Acad., Sci., **68**:1372, 1971.

35. Zbar, B. and Tanaka, T.: Immunotherapy of Cancer: Regression of Tumors after Intralesional Injection of Living Mycobacterium Bovis. Science, **172**:271, 1971.

36. Zukowski, C. F., Kullen, D. A., Ginn, E., Matter, B., Lucas, D. O. and Seigler, H. F.: Transplanted Carcinoma in an Immunosuppressed Patient. Transplantation, **9**:71, 1970.

Discussion

Dr. Richard E. Wilson (Boston): I would like to congratulate the authors of this paper on a very careful approach in this difficult area, particularly the sophisticated monitoring technics they have studied since I believe this is the key to better utilization of such immune therapy protocols.

Last year at these meetings, Dr. Godrick and I presented some of our studies with an immune therapy model that utilized syngeneic tumor cells for the treatment of minimal residual disease after surgical excision of the primary.

We determined that there was a critical dose of antigen in the form of live radiated or neuraminidase treated cells that could either increase immune reactivity and eliminate potential metastases, or stimulate the development of blocking factors with the increased incidence of metastases. Further studies in our laboratories continue to confirm this concept.

I would like to ask the authors how they determined the dosage of autochthonous tumor cells in the Stage 4 patients and were there any patients made worse after autochthonous tumor therapy? Did any of the patients in Stage 4 develop blocking antibodies after therapy that had not had them before therapy?

Dr. Donald Lee Morton (Los Angeles): I was struck by the similarity in the response rate that Dr. Seigler reports with his combination form of immunotherapy to what we have seen with BCG alone intralesionally. We have a 2-year tumor free survival in people who have disseminated disease of 25%. It is interesting that we, too, have not seen any complete or permanent regression in patients who have metastases in the brain or visceral organs but have seen good results in those with skin, subcutaneous tissue or regional lymph node metastases. Therefore, I wondered if he has any evidence that the combination program of immunotherapy is any better than the much simpler BCG alone.

Secondly, I would like to ask what *in vitro* evidence he has to show that stimulation of lymphocytes by autochthonous tumor cells does in face increase their cytotoxic effects upon tumor cells. We have done considerable work with this over the past couple of years and find that the conditions for *in vitro* sensitization are very critical and that the ratio of tumor cells to lymphocytes is very important. I wondered if they had any similar findings.

Dr. H. F. Seigler (Closing): In reply to Dr. Wilson, we have not been able to do a dose response in the human system. The control study that Zbar and Rapp have done in the guinea pig model with BCG does not exist in man.

We have looked at the response and activation of autologous lymphocytes by the x-irradiated autochthonous tumor cells. That is not a good measurement because we do not know exactly what it means. A ratio of one-to-one seems to be as good for stimulation as a ratio of one-to-two, one-to-three, or one-to-four, so we have empirically relied on a one-to-one mixture.

We have one patient that did convert to blocking when no blocking was present before treatment and this patient did become clinically worse. I think perhaps we could have stimulated blocking antibody and caused a worsening of the patient's metastatic disease; at least the clinical course did correlate with what we could measure *in vitro*.

In response to Dr. Morton's two questions, BCG versus the staged treatment, we really have no indication that ours is a bit better than BCG alone and we have talked about this before and it is quite interesting in that there is only about a 1 or 2% difference and there is a lot more labor involved in the staged therapy.

This could be added to by stressing that what we were trying to do was to look at mechanisms and so it seemed to us that we ought to study non-specific as well as specific responses of multiple aspects of the immune system.

In other words, what was the "T" cell response, the "B" cell response, the "T" and "B" cell interaction as well as the macrophage response? Also one must ask what role does humoral immunity play?

I think we have posed a number of questions but I cannot say that we have come up with any more suggestions than those that were presented in the slides. We could induce specific cellular immunity by stages 3 and 4 which we did not regularly observe in stages 1 and 2. BCG may give immunity as tested by skin test response to PPD but not to mumps, oidiomycin, etcetera and so this is why we proceeded with specific stimulation.

We do not have any good evidence that you can get increased cellular lysis by sensitization. We have looked at it by sensitizing the lymphocytes with unrelated lymphocytes and this seems to work as well as sensitizing the patient's lymphocytes against either an allogeneic melanoma cell or an autochthonous melanoma cell.

I think there is a tremendous complexity to the concert of cellular and humoral events that are taking place and we just do not understand it, but I think this is a tremendous area for investigation.

Surgical Resection and Adjunctive Immunotherapy for Selected Patients with Multiple Pulmonary Metastases

DONALD L. MORTON, M.D., WILLIAM L. JOSEPH, M.D.,
ALFRED S. KETCHAM, M.D., GLENN W. GEELHOED, M.D.,
PAUL C. ADKINS, M.D.

From the Divisions of Oncology & Thoracic Surgery,
University of California, Los Angeles, California;
Surgery Branch, N.C.I., Bethesda, Maryland and
Department of Surgery, George Washington University,
Washington, D.C.

LOGIC might suggest that the presence of pulmonary metastases would indicate disseminated malignancy uncontrollable by surgical treatment. However, many patients dying with pulmonary metastases have no other foci of disease detectable upon autopsy.[9,24] Furthermore, the 5-year survival rates in patients undergoing surgical resection of metastatic pulmonary lesions are often better than results obtained following surgical treatment of primary bronchogenic carcinoma.

Some controversy exists on the indications for resection of pulmonary metastatic disease. Many surgeons believe that pulmonary resection is indicated in patients with solitary metastatic lesions that appear after a prolonged interval following removal of the primary neoplasm in patients who have metastases limited to the lungs.[1,6,8–13,16,17,19,23] Most surgeons do not consider surgical treatment for patients who have multiple pulmonary metastases, especially if bilateral. However, as has been pointed out by others, the results of surgical resection for patients with multiple metastases rival those reported in patients with solitary lesions.[20,22] Furthermore, many patients who are subjected to thoracotomy for apparently solitary lesions are found to have multiple small subclinical metastases not detectable on radiological examination. Therefore, a re-evaluation of surgical treatment for multiple pulmonary metastases is indicated. Since approximately 30% of patients with malignant disease will have pulmonary metastases at some time during their clinical course, it is important to have some criteria for the selection of these patients who would most benefit from pulmonary resection.

In a preliminary report we previously suggested that measurement of the tumor doubling time appears to provide an accurate method for judging the biological aggressiveness of malignancy in a given patient.[14] This measurement may be an important indicator for those patients who might benefit from resection of the pulmonary metastases whether solitary or multiple.

The purpose of this report is to evaluate surgical treatment for multiple pulmonary metastatic lesions and to discuss adjuvant immunotherapy of selected patients undergoing resection of the pulmonary disease.

Materials and Methods

The patients included in this study were those seen by the authors in the Surgery Branch of the National Cancer Institute and Thoracic Surgical Services of George Washington University Hospital, and the Center of Health Sciences of the University of California at Los Angeles. We have approached pulmonary metastatic disease aggressively, attempting to resect most lesions if technically operable.

This report concerns 60 consecutive patients who were subjected to thoracotomy and resection of metastatic lesions.

Nineteen patients were treated with adjunctive immunotherapy following resection of their pulmonary metastases during the past 3 years. Immunotherapy was ad-

---

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25–27, 1973.

Supported by USPHS Grants CA12582, CA05262, CA12285 and grants from the California Institute for Cancer Research, the American Cancer Society and the Surgical Services, Sepulveda Veterans Administration Hospital.

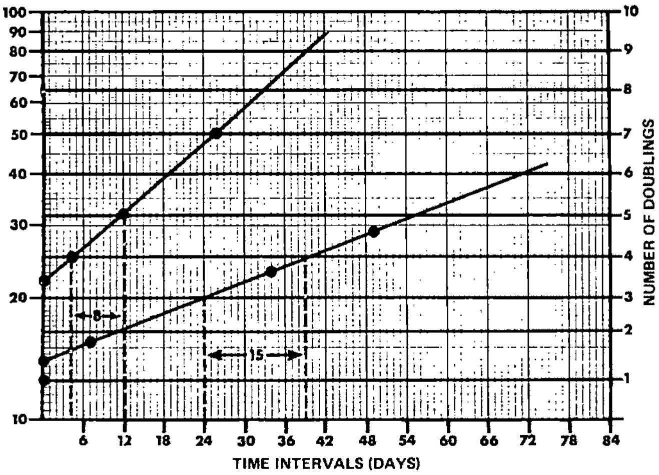


FIG. 1. Method of plotting tumor doubling time based upon the direct measurement of the changing diameters of metastatic pulmonary nodules. (Reprinted from Joseph, Morton, Adkins: J. Surg. Oncol. 3:143, 1971).

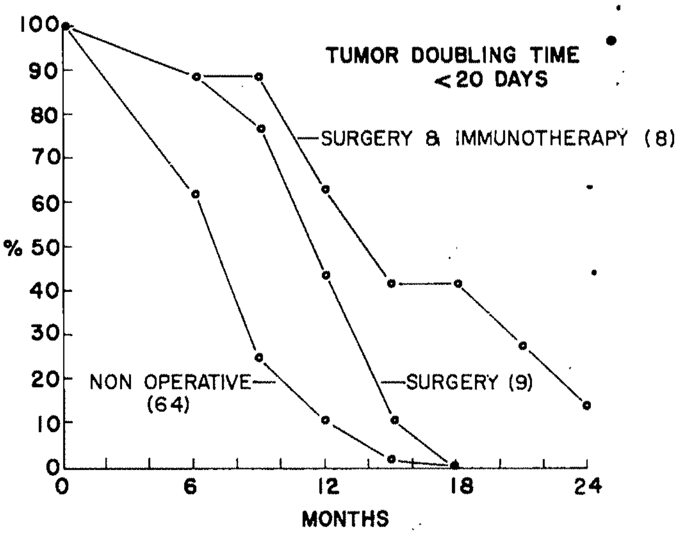


FIGURE 2.

ministered by methods previously described using a vaccine prepared from irradiated autologous tumor cells mixed with BCG.[18]

The methods used for measurement of the tumor doubling time (TDT) was reported previously.[2,3,14,15] Briefly, by using successive chest roentgenograms the changing diameters of each nodule are plotted on semilogarithmic paper against time and days between observations (Fig. 1). A line is drawn between the points; the slope of this line represents the rate of tumor growth. As this line crosses any two doubling lines, the horizontal distance in between represents the TDT in days. All patients had at least three serial measurements for each metastatic nodule. The TDT was calculated for those lesions that were clearly delineated on chest roentgenogram.

The survival rate of the 60 patients undergoing surgical resection of the metastatic disease was compared with a group of 89 patients who received no treatment or who received chemotherapy for the pulmonary metastases. Table 1 shows the range of tumor doubling times according to the pathologic diagnosis and the number of patients in each category. Of note was the considerable variation in tumor doubling time for each histologic type of neoplasm. Since the cell type of the primary neoplasm was not characterized by a particular tumor doubling time, these patients were reclassified into three groups on the basis of growth rates as measured by the tumor doubling time.

TABLE 1. *Types of Neoplasms in Operative and Non-operative Treatment Groups*

Type of Neoplasm	Surgical Resection Patients		Surgical Resection Range TDT	Non-Operative Treatment Patients		Non-Operative Treatment Range TDT
Carcinoma	20	33%	21–360	33	38%	11–360
Sarcoma	34	57%	13–360	50	55%	5–360
Miscellaneous	6	10%	11–55	6	7%	13–80
Total	60	100%		89	100%	

Our previous report showed that the growth rate and eventual prognosis correlated well when the TDTs were arbitrarily divided into three groups based upon a TDT of less than 20 days, 20-40 days, and greater than 41 days. Consequently, all patients with multiple metastatic foci were classified into three groups based upon their TDTs regardless of the histologic type of the neoplasms.

There were 10 patients with multiple pulmonary metastases in whom tumor growth rate varied extensively. Their calculated TDTs did not fall into a single category. These patients were grouped according to the growth rate of their fastest growing lesions, because as previously reported, prognosis appears to be determined by the fastest growing lesions rather than the slower growing lesions.[15]

The accumulative survival of patients in these three groups was plotted by the actuarial life table method.[5] The operative and non-operative groups are compared in Figures 2, 3, and 4. The three groups treated by surgical resection are compared in Figure 5.

Results

Twenty-seven patients had multiple lesions bilaterally whereas 33 had multiple nodules confined to one lung. Eighty-seven thoracotomies were performed in 60 patients. In most cases, the metastases were easily located beneath the pleura and were removed by wedge resection. Wedge resections only were performed in 71 thoracotomies. Twenty-six patients underwent staged bilateral thoracotomies and one patient had a simultaneous bilateral thoracotomy. Patients presenting with simultane-

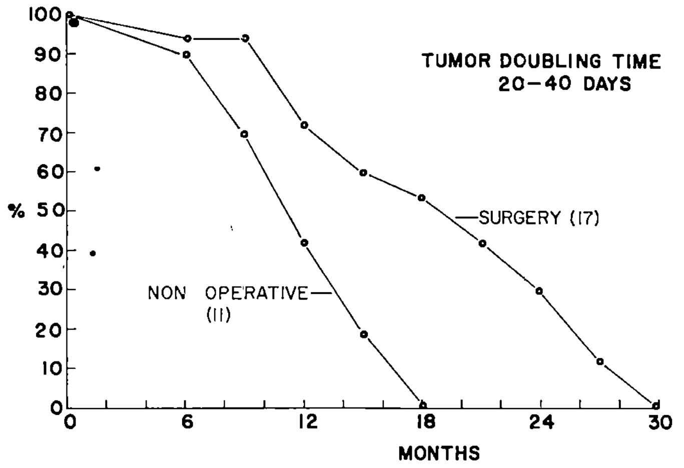


FIGURE 3.

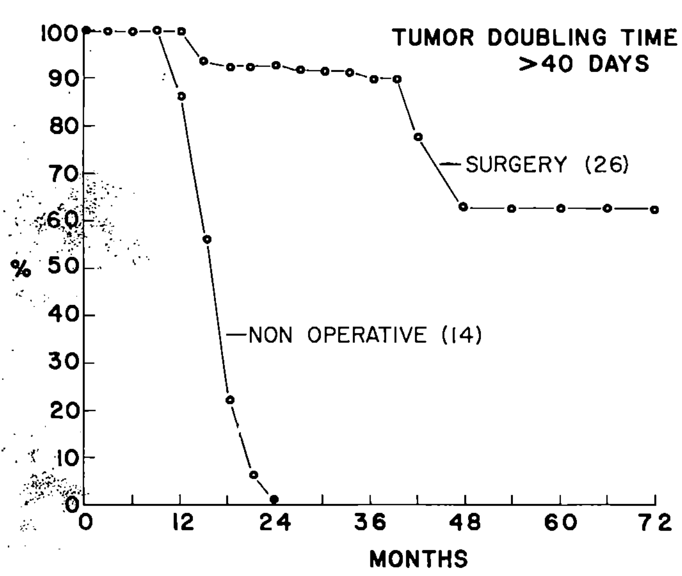


FIGURE 4.

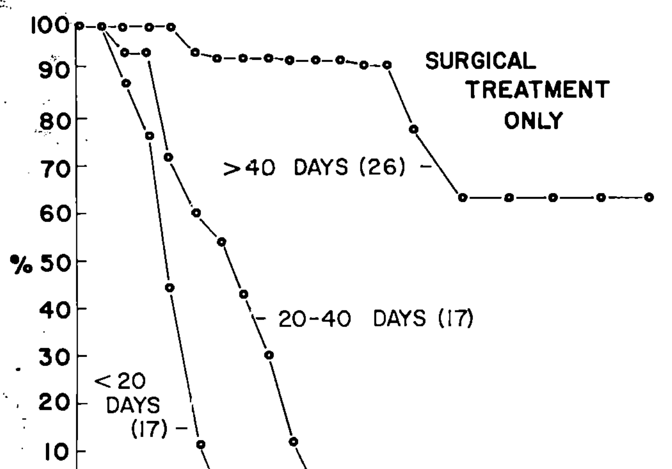


FIGURE 5.

ous bilateral pulmonary metastases usually underwent thoracotomies staged at 10-30 days between resections. Other patients had metastatic lesions in one lung which were resected, only to return, after several months or years, for resection of metastatic lesions in the opposite lung.

The number of wedge resections performed in one lung varied between three and 28. Because of their subpleural location, it was possible to detect lesions as small as 2 millimeters in diameter. Preoperative chest X-rays and tomograms accurately detected lesions upwards from 1 cm. in size. However, additional smaller subpleural metastases often were not radiographically apparent. Pulmonary tissue was preserved by resecting 85-90% of the subpleural lesions with a wedge resection of 2 cm. of normal surrounding lung. Major pulmonary resections were necessary in only 16 patients. Lobectomy was performed in 13 patients and three had pneumonectomy. There was one operative death in the 87 thoracotomies.

An extensive preoperative evaluation was carried out on all patients to exclude other sites of metastatic disease. This work-up included full chest tomograms to evaluate the multiplicity of metastatic nodules, metastatic bone series, radioisotope scans of the bone, brain, and liver, and liver function tests. Immunocompetence was tested by the DNCB skin test in those patients seen during the past 3 years.[7] Patients with equivocal liver function tests and liver scans underwent hepatic angiography. Exploratory laparotomy was performed in 10 patients as an added precaution to exclude hepatic metastases in patients with equivocal hepatic radioisotopic scans or angiograms. At the time of thoracotomy, four patients underwent transdiaphragmatic exploration of the peritoneal cavity and palpation of the liver, while six patients had transabdominal exploratory laparotomies prior to thoracotomy.

The accumulative survival of patients with tumor doubling times of less than 20 days is compared in Figure 2. In the group of 64 patients who received non-operative management, 63% were alive at 6 months, 11% at 1 year, and none beyond 18 months. Of the nine patients who had surgical resection alone, 89% were alive at 6 months, 44% at 1 year, but all were dead by 18 months. Of the eight patients who received adjuvant immunotherapy in addition to surgical resection, 88% were alive at 6 months, 63% at 1 year, 40% at 18 months, and 13% at 24 months.

Although the numbers of patients in the operative groups are small, there appears to be a modest prolongation of survival in this group. If the two groups receiving surgical therapy are combined, the 1 year survival rate is 53%, or nine of 17 patients, in those receiving surgical treatment compared to 11%, or seven of 64 patients, in the non-operative group. These differences are statistically significant ($p = <0.05$). The number of patients receiving immunotherapy is too small at this point to definitively evaluate the effectiveness of adjunctive immunotherapy in prolonging survival. However, at this time, the prolongation in survival appears to be relatively modest.

The accumulative survival of patients with tumor doubling times of 20-40 days is compared in Figure 3. Of the 11 patients receiving non-operative treatment, 90% were alive at 6 months and 45% survived 1 year. No patients were alive beyond 18 months in this group. Of the 17 patients treated by surgical resection of the pulmonary metastases, 94% were alive at 6 months, 72% at 1 year, 54% at 18 months, 30% at 24 months, but no patient survived beyond 30 months. Comparing the 50% survival point, there is a life prolongation from 11 months to 18 months by surgical treatment. Thus, patients undergoing surgical resection of the metastatic lesions survived an average of 7 months longer than the non-operative patients.

The accumulative survival of patients with a tumor doubling time greater than 40 days is summarized in Figure 4. All patients in the non-operative group survived at least 9 months after the onset of pulmonary metastases. Eighty-six per cent were alive at 1 year but none survived beyond 2 years. In contrast, survival of patients who underwent pulmonary resection was considerably increased. At 2 years following operation when all of the non-operative treated patients were dead, 97% of those undergoing surgical resection were still alive. The differences between these groups are significant at the $p = <0.01$ level. In fact, 63% of patients who have been followed for more than 5 years in the surgically treated group with TDT > 40 days are still alive. Most patients in this group are free of disease at 5 years after surgical resection. This was true despite the fact that 14 of these 26 patients had bilateral pulmonary metastases and underwent bilateral thoracotomies. The results of surgical treatment alone in this group are so good that it is difficult to evaluate the influence of adjunctive immunotherapy in the eight patients who received this treatment.

Discussion

This study clearly indicates that selected patients with multiple pulmonary metastases can be significantly benefited by aggressive surgical treatment even with bilateral disease or multiple metastases in the same lung. Measurement of the tumor doubling time appears to be a remarkably accurate means of selecting those patients who will benefit most from aggressive surgical treatment. Those patients with a tumor doubling time of greater than 40 days may have a 63% 5-year survival rate following surgical resection whereas patients managed by non-operative treatment usually will not survive more than 2 years. Conversely, patients with a tumor doubling time of less than 40 days show only a 7-month increase in survival from surgical treatment beyond that expected from non-operative management. Adjunctive immunotherapy slightly increased survival beyond that obtained by operation alone in this group of patients. We anticipate new methods of immunotherapy that may improve these results.

Based upon the tumor doubling time, the striking differences in the results of surgical treatment in these patients appears to indicate a fundamental characteristic in the tumor-host relationship of each patient.[14,21] The growth rate of each patient's tumor was dependent upon the interrelationships of the immune defense mechanisms and the intrinsic growth potential of the neoplasm. The improved results in patients with a prolonged tumor doubling time appears to indicate a favorable host immune response to the neoplasm. Patients with a rapid tumor doubling time are more likely to have metastatic lesions at other sites such as the liver, brain, or bone, so that treatment of the pulmonary metastases results in relatively little improvement in survival. In contrast, patients with prolonged tumor doubling time are more likely to have metastases limited to the lungs and aggressive treatment of the pulmonary metastases results in greatly prolonged survival.

Evidence that the patient's immune response is a significant factor in determining the growth rate of the neoplasms comes from studies of complement fixing antibody titers in patients with metastatic sarcomas. In these cases, we found a good correlation between a high titer of antibody and a slowly growing sarcoma. Patients with pulmonary metastases who had titers of 256 or greater usually had tumor doubling times of greater than 40 days, whereas patients with tumor doubling times of less than 20 days had little or no detectable antisarcoma antibody in their serum. Thus, the time of tumor doubling is a measure of the biological aggressiveness of a neoplasm in a given patient which can account for both the intrinsic growth potential of the neoplasm and the inhibiting influence of the host's immune defenses. Therefore, the patient's tumor doubling time can be used as a criterion for pulmonary resection with assurance of a favorable prognosis. For this reason, we urge that patients in whom metastatic pulmonary lesions demonstrate a tumor doubling time greater than 40 days be considered for surgical resection even though the lesions are multiple and bilateral.

In patients with multiple metastases, it is very important to measure the tumor doubling time of all visible lesions. Approximately 16% of patients will have wide variations in the TDT of some of their metastatic lesions. Since prognosis depends upon the TDT of the fastest growing lesions, such measurements can be critical. A maximum delay of 1 month is necessary to determine the tumor doubling time of pulmonary metastases. In this time, three observations can be made. An initial X-ray, one at 2 weeks, and one at 1 month will show significant growth in lesions with a tumor doubling time of less than

40 days. Sometimes, these rapidly growing lesions, make a TDT calculation possible in a 2-week observation period.

It must be emphasized that no patient should be considered for resection of pulmonary metastases without extensive preoperative evaluations to exclude metastatic foci at other sites. We believe it is important to include a measurement of the patient's immune response to a new antigen such as DNCB in this work-up since our experience has shown that patients who are anergic to this chemical have metastases at other sites even when these lesions are not clinically detectable. In addition to liver function tests, metastatic bone series, and radioisotopic scans of the bone, brain, and liver, we advocate full chest tomograms to detect any additional lesions that might be missed on plain chest films.

Certain technical aspects of the operative procedure deserve emphasis. We believe that patients with bilateral metastases should have resection on the least involved lung first. In this way, the extent of disease on the minimally involved side is known at the time of thoracotomy on the opposite side when one may be faced with a major pulmonary resection such as bilobectomy or pneumonectomy. In addition, the patient has more adequate pulmonary function for the second procedure than if the pneumonectomy or bilobectomy was done first.

We have found the following operative technic to be useful. Upon entering the chest, a careful search is made for mediastinal or hilar lymph nodes which, if found, are removed for frozen section examination. Following this, a careful search is made for pulmonary metastatic lesions. Each metastases is marked with a suture to indicate its location. A majority of the metastatic lesions are subpleural in location for unknown reasons. It is of interest, however, that approximately 90% of pulmonary metastases in animal neoplasms are also subpleural in location. Whatever the explanation, this location greatly simplifies the surgical excision.

Extreme care is taken in examining the lung in both the inflated and deflated conditions. The exploration and search usually takes at least 15-20 minutes during which time the surgeon carefully marks each lesion he is able to palpate. Following this, he has his first and second assistants carefully examine the lungs for metastases. Not infrequently, the assistants find one or two additional metastatic lesions. All of the metastatic lesions should be detected and marked prior to resection of any one lesion because the resection inevitably results in artifacts at the suture line and atelectasis which may be mistaken for additional lesions.

After exploration is completed, and all metastatic lesions have been marked with sutures, it is easier to plan the extent of resection and make the decision between multiple wedge resections and a lobectomy. The subpleural location of the metastases makes a wedge resection feasible in most instances. We have found that the mechanical stapling device is an extremely useful instrument in patients who need multiple wedge resection. Its use is facilitated if the metastasis is outlined with clamps such as Bouie hemorrhoid clamps. The excision is performed with the mechanical stapling device beyond the clamps. This insures an adequate margin of normal lung parenchyma beyond the metastases. Using this technic, local recurrence of metastases at the suture line has been kept to a minimum. In fact, we have had only one incident of local recurrence and two incidences of missed metastatic lesions that required additional thoracotomies in the 26 patients with tumor doubling time greater than 40 days who have survived for long periods.

Summary

Evaluation of the results of surgical treatment in 60 patients with multiple pulmonary metastases indicates that aggressive surgical resection is indicated when tumor doubling time is greater than 40 days. Approximately 60% of these patients will survive 5 years after operation; therefore, these patients should undergo pulmonary resection even when bilateral thoracotomy is necessary. Conversely, patients with tumor doubling time of less than 40 days were only slightly benefited by surgical resection and were dead of the disease within 2 years. The marked differences in surgically treated patients with tumor doubling time of less than 40 days when compared to those with a TDT of greater than 40 days is illustrated by the fact that only 6% of patients with tumor doubling time less than 40 days survived 2 years while 94% of those with tumor doubling times greater than 40 days survived beyond 2 years. Fifty-four per cent of patients in the greater than 40-day group required bilateral thoracotomy because of bilateral metastatic lesions.

These differences in the results of surgical treatment appear to be due to differences in the biological aggressiveness of the neoplasms in these two groups of patients. Patients with prolonged tumor doubling time are less likely to develop extra pulmonary metastatic lesions and, therefore, resection of the present pulmonary metastases greatly improves survival. In contrast, patients with tumor doubling times less than 40 days invariably have extra pulmonary metastatic lesions which are not detectable on clinical examination and eventually contribute to their death. Thus, pulmonary resection in this group of patients results in only a minor prolongation of survival. Although immunotherapy appears to prolong survival somewhat in these patients, they all eventually died of the disease. Hopefully new methods of immunotherapy may improve these results.

References

1. Alexander, J. and Haight, C.: Pulmonary Resection for Solitary Metastatic Sarcomas and Carcinomas. Surg. Gynecol. Obstet., 85:129, 1947.
2. Collins, V. P., Loeffler, R. K., and Tivey, H.: Observations on Growth Rates of Human Tumors. Am. J. Roentgenol., 76:988, 1956.
3. Collins, V. P.: Time of Occurrence of Pulmonary Metastases from Carcinoma of Colon and Rectum. Cancer, 15:387, 1962.
4. Cliffton, E. E., Gupta, T. D. and Pool, J. L.: Bilateral Pulmonary Resection for Pulmonary or Metastatic Lung Cancer. Cancer, 17:86, 1964.
5. Cutler, S. J. and Ederer, F.: Maximum Utilization of the Life Table Method in Analyzing Survival. J. Chron. Dis., 8:699, 1958.
6. Ehrenhaft, J. L.: Pulmonary Resections for Metastatic Lesions. Arch. Surg., 63:326, 1951.
7. Eilber, F. R., and Morton, D. L.: Impaired Immunologic Reactivity and Recurrence Following Cancer Surgery. Cancer, 25:362, 1970.
8. Fallon, R. H. and Roper, C. L.: Operative Treatment of Metastatic Pulmonary Cancer. Ann. Surg., 166:263, 1967.
9. Farrell, J. T.: Pulmonary Metastases: A Pathologic, Clinical Roentgenologic Study Based on 78 Cases Seen at Necropsy. Radiology, 24:444, 1935.
10. Gliedman, M. L., Horowitz, S. and Lewis, F. J.: Lung Resection for Metastatic Cancer: 29 Cases From the University of Minnesota and a Collected Review of 264 Cases. Surgery, 42:521, 1957.
11. Groves, L. K. and Effler, D. B.: Surgery for Metastatic Neoplastic Disease in the Lung: Review of 38 Cases. Cleveland Clin. Quart., 23:16, 1956.
12. Habein, H. C. Clagett, O. T. and McDonald, J. R.: Pulmonary Resection for Metastatic Tumors. Arch. Surg., 78:716, 1959.
13. Jensik, R. J. and Van Hazel, W.: The Surgical Treatment of Metastatic Pulmonary Lesions. Surgery, 43:1002, 1958.
14. Joseph, W. L., Morton, D. L. and Adkins, P. C.: Prognostic Significance of Tumor Doubling Time in Evaluating Operability in Pulmonary Metastatic Disease. J. Thorac. Cardiovasc. Surg., 61:23, 1971.
15. Joseph, W. L., Morton, D. L. and Adkins, P. C.: Variation in Tumor Doubling Time in Patients with Pulmonary Metastatic Disease. J. Surg. Oncol., 3:143, 1971.
16. Kelley, C. R. and Langston, H. T.: Treatment of Metastatic Pulmonary Malignancy. J. Thorac. Surg., 31:298, 1956.
17. Moersch, R. N. and Clagett, O. T.: Pulmonary Resection for Metastatic Tumors of the Lungs. Surgery, 50:579, 1961.
18. Morton, D. L., Eilber, F. R., Joseph, W. L., Wood, W. C. Trahan, E. and Ketcham, A. S.: Immunological Factors in Human Sarcomas and Melanomas: A Rational Basis for Immunotherapy. Ann. Surg., 172:740, 1970.
19. Ochsner, A., Clemmons, E. F. and Mitchell, W. T.: Treatment of Metastatic Pulmonary Malignant Lesions. J. Lancet, 83:16, 1963.
20. Payne, W. S., Clagett, O. T. and Harrison, E. G.: Surgical Management of Bilateral Malignant Lesions of the Lung. J. Thorac. Cardiovasc. Surg., 43:297, 1962.
21. Spratt, J. S., Jr. and Spratt, T. L.: Rates of Growth of Pulmonary Metastases and Host Survival. Ann. Surg., 159:161, 1964.
22. Thomford, N. R., Woolner, L. B. and Clagett, O. T.: The Surgical Treatment of Metastatic Tumors in the Lungs. J. Thorac. Cardiovasc. Surg., 49:357, 1965.
23. Wilkins, E. W., Burke, J. F. and Head, J. M.: The Surgical Management of Metastatic Neoplasms in the Lung. J. Thorac. Cardiovasc. Surg., 42:298, 1961.
24. Willis, R. A.: The Spread of Tumours in the Human Body, London, 1952, Butterworth & Co., Ltd.

DISCUSSION

DR. EDWARD J. BEATTIE, JR. (New York City): I think it is a major contribution that Dr. Morton has been able to segregate a group of multiple pulmonary metastases, and then get a 60% 5-year survival rate. The primary tumor must be under control for this to be done.

I thought you might like to hear a progress report on the studies that have been going on at our institution with osteogenic sarcoma of the extremities in children.

This is a tumor which is treated with amputation and thus has an advantage, that the primary lesion is under control. Dr. Ralph Marcove reviewed a series of 145 patients under 21 years with osteogenic sarcoma in the extremities, and found that one of six was cured by amputation. Fifty per cent of those not cured by amputation were dead in 12 months. Eighty-eight per cent were dead in 24 months, and 95% were dead in 36 months.

Dr. Marcove used autologous tumor vaccines made from the tumor at the time of amputation in a series of 15 patients. He had nine patients or 40% who remained free of disease at 36 months. That is a considerable improvement, but it is very small series which needs expansion.

Two years ago we reported a series of 29 patients with pulmonary metastases of osteogenic sarcoma. At operation, seven patients had showers of tumors and it was impossible to clear the lungs. In 22 patients, it was possible to remove all of these tumors. In those 22 patients, we have now done 61 thoracotomies, removed over 150 metastases, and six of 22 are well 5 years after amputation.

One of our best cases was a girl who had had a hip disarticulation with a negative chest X-ray. Four months later she had nine metastases. After four thoracotomies, and removal of 11 metastases, there is no evidence of disease 7 years after amputation, and she has graduated from college and married.

Many of our children have too many metastases to remove, and we have been using intensive chemotherapy. Dr. Jerry Rosen of our pediatric department, who treats disseminated osteogenic sarcoma patients, has had marked regression in nine of ten patients.

We have monitored the immune status of these children, and found that they have remained DNCB positive and maintained their skin reactivities until they were terminal. Even then some of them maintained a positive DNCB.

Presently, we are trying to see whether immunotherapy and chemotherapy with operation will improve our results. It is possible to cure one of six with amputation; perhaps another 20 to 25% with pulmonary surgery alone; and possibly with the addition of immunotherapy and chemotherapy this cure rate can be improved.

DR. WILLIAM S. BLAKEMORE (Philadelphia): For some time we have been interested in immunotherapy. Following some disappointing results with tumor injection of preparations from the patients' tumor, particularly melanoma, in the middle 1950's, we have continued experimental work with a group of investigators associated with Dr. Stuart Mudd.

They found non-specific activation of the macrophage system in mice by the injection of certain bacterial substances, particularly from staphylococci. These antigens have also shown protection against infections, such as specific viral infections.

We have also been able to demonstrate with Dr. Kwan Park that surgical operations and some common drugs, such as barbiturates, and probably some of the anti-cancer drugs commonly used decrease some functions of the lymphocytes as measured by laboratory technics. We do not have a good method to measure macrophage activity in man which would be valuable information.

We have looked at the reactions to DCNB by some patients with malignancy and I would particularly ask Dr. Morton if he has some other criteria which he thinks might be promising in measuring the immune response in man which might be particularly effective against cancer, particularly as it involves cellular hypersensitivity which seems to be a promising approach at this time.

We have been using bacterial toxins similar to that of "Coley's toxin" and we think bacterial antigens deserves additional clinical trails. We are not using "Coley's toxin" as he uses mixed bacterial toxins but we're using the staphyoccal phage lysate because the staphyloccus apparently has some activity for producing cellular hypersensitivity.

A large number of bacterial toxins may promote non-specific immunity and it would be of interest to know from Dr. Morton's background and studies whether he has found factors such as the immune globulin or others that might be of value in predicting host resistance against cancer.

DR. DONALD L. MORTON (Closing): Dr. Blakemore, I think BCG is only one of a wide variety of substances that have the ability to non-specifically enhance the cellular immunity.

These include corynebacterium parvum, the staphylococcus or mixed bacterial toxins, BCG, and some of the polynucleotides. Many of these substances have the ability to non-specifically enhance immunity to a large variety of antigens, whether they be viral, bacterial, fungal or tumor antigens.

However, in the animal studies, it is striking that although there is some activity when these things are used systemically, much better immunity is induced when these substances injected at the same site as the growing tumor or with tumor antigen.

It's important to emphasize that operation, chemotherapy, steroids, and even radiation therapy, have the ability to depress immune reactivity. An operation may turn off cellular immunity for several weeks. For this reason, the DNCB skin testing should be done in the preoperative patient because if it is done in the postoperative period there may be a spurious negative test and it is the presence of anergy that is important; if the patient has no immune capability at all, then he usually does not do well.

However, the patient may be able to respond to DNCB which is a general antigen but still have some disarrangement in his specific immune response to the tumor antigens so that even with a positive DNCB test there is not always protection against recurrence.

I would like to emphasize a point made by Dr. Beattie that makes some of you wonder how we can resect these multiple metastatic lesions. I think the record that I have is 27 in one lung and 28 in the other. The reason this is possible is shown on this slide. For some reason, possibly having to do with blood flow to the lung, 80 to 90% of these metastases are subpleural in their location, so that it is easy to remove them with a wedge excision.

The subpleural location of these metastases is an interesting phenomenon because the same thing is seen in animals that have metastases to the lungs. Here too about 90% of the metastases go to the subpleural location which is fortunate from the standpoint of resecting them. We find the mechanical stapling device very useful in patients with multiple lesions. So, our strategy is to conserve as much functioning pulmonary tissue as possible and this can usually be done by the multiple wedge resections.

A New Approach to Colonic Polyps

WILLIAM I. WOLFF, M.D.*
HIROMI SHINYA, M.D.**

THE KEY to the management of rectal and colonic polyps is their association with carcinoma. Although polyps may come to the clinician's attention as the result of bleeding and, occasionally, by producing intussusception, it is the *presence of* or *potential for* cancerous change that is the determining factor in their management. For treatment of recto-sigmoid polyps above the level of the peritoneal reflection and for colonic polyps, the clinician must balance the malignant potential against the hazards of surgical removal or the risks inherent in a program of prolonged observation.

The problems posed by these alternate management regimens are well-recognized by experienced surgeons and clinicians. They may be outlined as follows:

Observation Program:

1. Radiation exposure associated with repeated barium enema studies.
2. Psychological strain of uncertainty on the patient.
3. Can growth or malignant change be identified accurately and early by radiologic means?
4. Are there additional undemonstrated polyps present?
5. Is there a separate undemonstrated cancer present?

Operative Program:

1. Operative morbidity and mortality—affected by patient's age, other disease processes, etc.
2. Limitations of frozen section at time of operation—incomplete, inconclusive, mutilates specimen, etc.
3. Additional polyps can be missed—even with operative coloscopy.
4. Additional polyps may become manifest at a later date.

A case history relevent to the last item is pertinent and not atypical.

From the Department of Surgery,
Beth Israel Medical Center, New York City

Case Report

OPM: A 53-year-old woman with recurrent rectal bleeding had two barium enema X-rays (one air contrast) both of which showed a small radiolucent defect in the proximal transverse colon. One year previously she had undergone trans-abdominal removal of benign polyps from the sigmoid and transverse colon. Postoperatively she had developed intermittent small bowel obstruction responding to conservative measures and later had to be rehospitalized for hepatitis. At colonoscopy, on present admission, the polyp seen radiologically in the transverse colon was removed endoscopically plus an undiagnosed 1.5 × 1.5 cm. polyp from the sigmoid colon.

With the development of the fiberoptic colonoscope it is now possible to examine directly the entire colonic lumen from the cecum to the anus in a very high percentage of individuals.[35,36,39] What remains to be determined is the safety of the method and its accuracy when applied on a large scale by individuals of varying skill and experience.[1,33] In our Endoscopy Unit well over 2,000 colonoscopic examinations have been performed with insignificant morbidity and without mortality. Our routine examination involves the use of the 106 cm. scope which generally reaches the transverse colon. The 186 cm. scope, which can be introduced well into the cecum, is employed when there are specific indications[34] (Fig. 2). Full penetration is possible with a surprisingly high degree of success by endoscopists of experience. Dr. Shinya has introduced a number of refinements of technic which has contributed to complete insertion of the long instrument.

Once the technic of colonoscopy has been mastered, the removal by endoscopic means of polypoid lesions anywhere in the colon can be accomplished with reasonable success[13,30,34,38] using two tools: (1) a simple adaptation of the tried-and-true electrosnare-cautery wire (Fig. 3) and (2) the tried-and-true principle of common

---

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25-27, 1973.

* Professor of Clinical Surgery, Mt. Sinai School of Medicine.

** Assistant Professor of Surgery, Mt. Sinai School of Medicine.

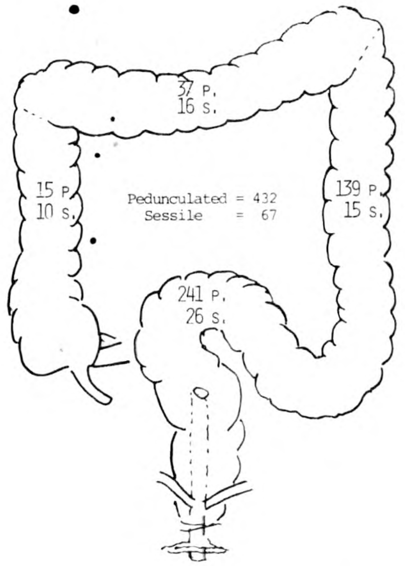


FIG. 1A. Gross morphology and distribution.

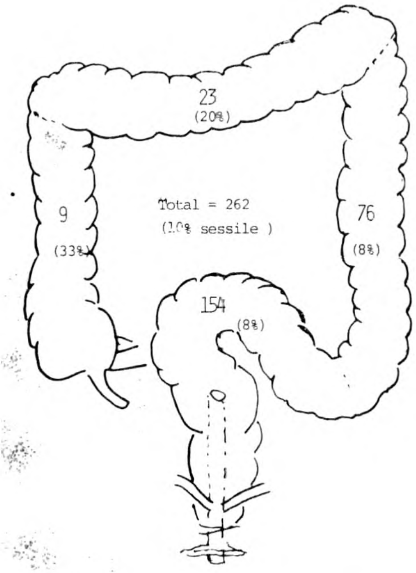


FIG. 1B. Adenomatous polyps—gross morphology and distribution. Percent sessile in parenthesis.

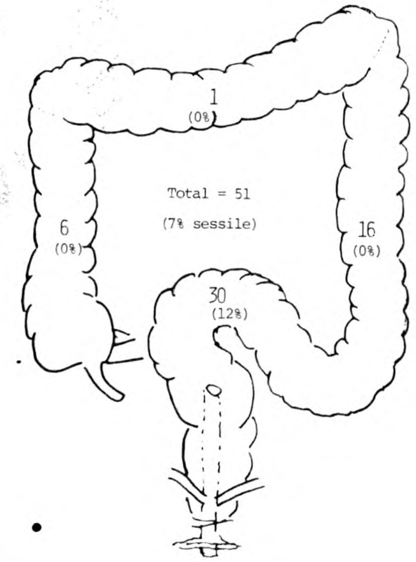


FIG. 1C. Villous polyps—distribution. Percent sessile in parenthesis.

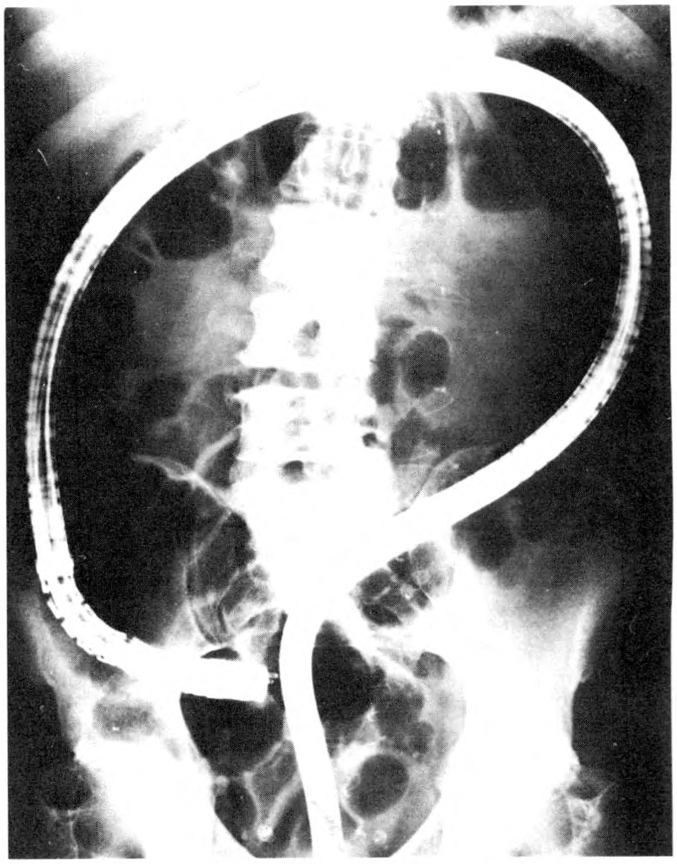


FIG. 2. Colonoscope in cecum.

sense.[34] We encountered only two patients in whom the polypoid lesions were not endoscopically accessible.

Grossly, polyps are regarded as pedunculated or sessile, although sometimes the stalk is obscured.[27] This aspect of gross morphology is more readily appreciated endoscopically when the bowel lumen is distended with air than in the flattened contracted surgical or autopsy specimen. Only 9.4% of the polyps were of the sessile type. An interesting, as yet not fully understood difference in distribution of sessile and pedunculated polyps becomes apparent when they are analyzed according to the histologic form, *i.e.* villous or adenomatous (Fig. 1).

By and large, polyps on a pedicle, fortunately the commoner type, can be resected most readily. Broad-based

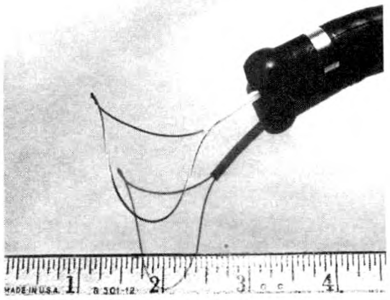


FIG. 3. Snare-cautery wire.

Table 1. *Polypectomy Procedures Per Patient*

First 499 Polypectomy Operations	
317	Had 1 Procedure
29	Had 2 Procedures
4	Had 3 Procedures
	Total patients 350

Table 2. *Polyps Removed Per Procedure*

First 499 Patient Procedures	Polyps per Procedure
300	1 Polyp
47	2 Polyps
17	3 Polyps
6	4 Polyps
6	5 Polyps
Total Procedures—376	Total Polyps—499

Table 3. *Polyps Sorted According to Size*

(First 499 Polyps) Size (Greatest Diam.)	No. of Polyps
0.5–0.9 cm.	105
1.0–1.9 cm.	266
2.0–2.9 cm.	91
3.0–3.9 cm.	31
4.0–4.9 cm.	4
5.0– cm.	2
	499

or sessile tumors present a more difficult but not unconquerable challenge.[34]

Data

We will present our findings on 499 colonic polyps removed endoscopically over a 26-month period. Only polyps one-half centimeter in diameter or over are included. Although a large number of smaller polyps were also removed during this period these are not included since they were invariably benign and their extirpation was an incidental event. The number of patients involved was 350 since a number of individuals had more than a single polyp removal at one or more endoscopic sessions (Table 1). The largest number of this size polyps resected at a single sitting was five (Table 2).

Sorting of the polyps removed according to size is shown in Table 3 and with respect to level and anatomical location in Tables 4 and 5. The largest polyps, as noted were 5 cm. in diameter (Fig. 15).

Complications

Two significant complications occurred. One patient bled moderately after removal of a wide based 3.5 cm. villous adenoma high in the sigmoid colon. The bleeding stopped spontaneously within 48 hours and the patient was discharged 2 days later. The other was a minimally symptomatic perforation which occurred after resection of a sessile 2 cm. polypoid carcinoma in the distal descending colon (Fig. 4). Retrospectively this total endoscopic resection was probably ill-advised. However, the patient did very well on conservative management, and when the bowel was segmentally resected 4 weeks later the pathologist could find no evidence of residual tumor.

Pathology

Table 6 shows the histologic diagnoses made on the polyps removed. The microscopic pathology of colonic polyps is a complicated and perplexing topic and one subject to a variety of interpretations.[4–7,11,16,21,22,26,31] For example, the majority of adult polyps have, up until recently, been regarded as being either of the adenomatous or the villous variety. We discovered a surprisingly large

Table 4. *Location of Polyps Measured by Distance from Anal Orifice*

(First 499) Polyps) Level (in cm.)	No. of Polyps
10–19	14
20–29	43
30–39	92
40–49	126
50–59	54
60–69	58
70–79	32
80–89	24
90–99	10
100–109	14
110–119	9
120–129	10
130–139	6
140–149	1
150–	6
	499

Table 5. *Location of Polyps by Colonic Segments*

(First 499 Polyps)	Pedunculated	Sessile	Total
Recto-Sigmoid	5	3	8
Sigmoid	236	23	259
Descending Colon	139	15	154
Splenic Flexure	8	5	13
Transverse	29	11	40
Cecum & Ascending Colon	15	10	25
	432	67	499

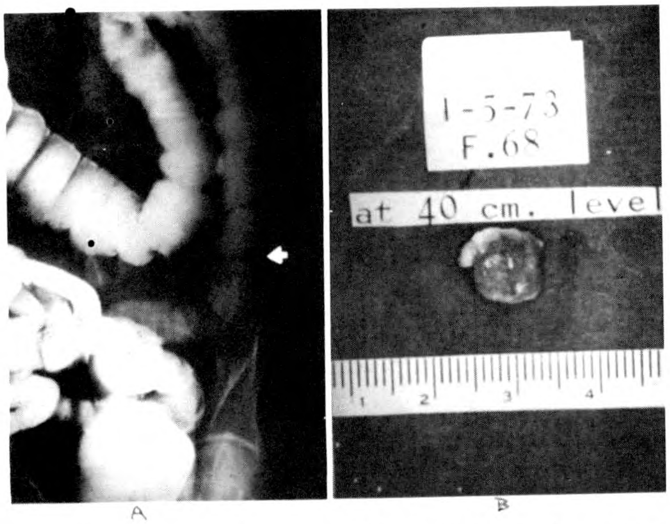


FIG. 4. Barium enema X-ray (A left) and endoscopically removed polypoid carcinoma (B right) of distal descending colon.

TABLE 6. *Histopathologic Diagnosis on Endoscopically Removed Polyps.*

(First 499 Polyps)		
Adenomatous Polyps		262
with "atypia"	14	
with superficial or focal carcinoma	5	
Villous or Papillary Adenoma		51
with "atypia" or carcinoma *in situ*	4	
with superficial carcinoma	7	
Mixed Villous and Adenomatous Polyps		108
with "atypia" or carcinoma *in situ*	10	
with superficial czrcinoma	5	
"Mucosal Polyps"		24
Miscellaneous (inflamm., fibrovascular, juvenile)		4
Unretrieved		33
Malignant "Polyps"		17
Polypoid adenocarcinoma	6	
Villous adenoma with invasive carcinoma	7	
Adenomatous polyp with invasive carcinoma	4	
		499

number in which both adenomatous and villous mucosal features (Fig. 5) could be identified in the same polyp—a fact which is beginning to emerge in the literature.[8,9,21,29,34] When early carcinomatous change occurs it is possible to demonstrate in which type of epithelium it originates.

The major problem is just what constitutes "malignancy" in a clinical sense. Our pathologists report readily, and with consistency, the full gamut of cellular alteration from "focal atypia" to "carcinoma *in situ*" to full blown but "superficial carcinoma." (Figs. 6-10) Omitting "atypia" and "carcinoma-*in-situ*" our incidence of "malignancy" in this context is 6.8%. The malignant potential of these various "preinvasive"[16] changes in terms of the patient is moot. We have taken the stand recommended by such eminent authorities as Welch,[31] Castleman[4,5] Morson[21,22] and others, that only when definite invasion,

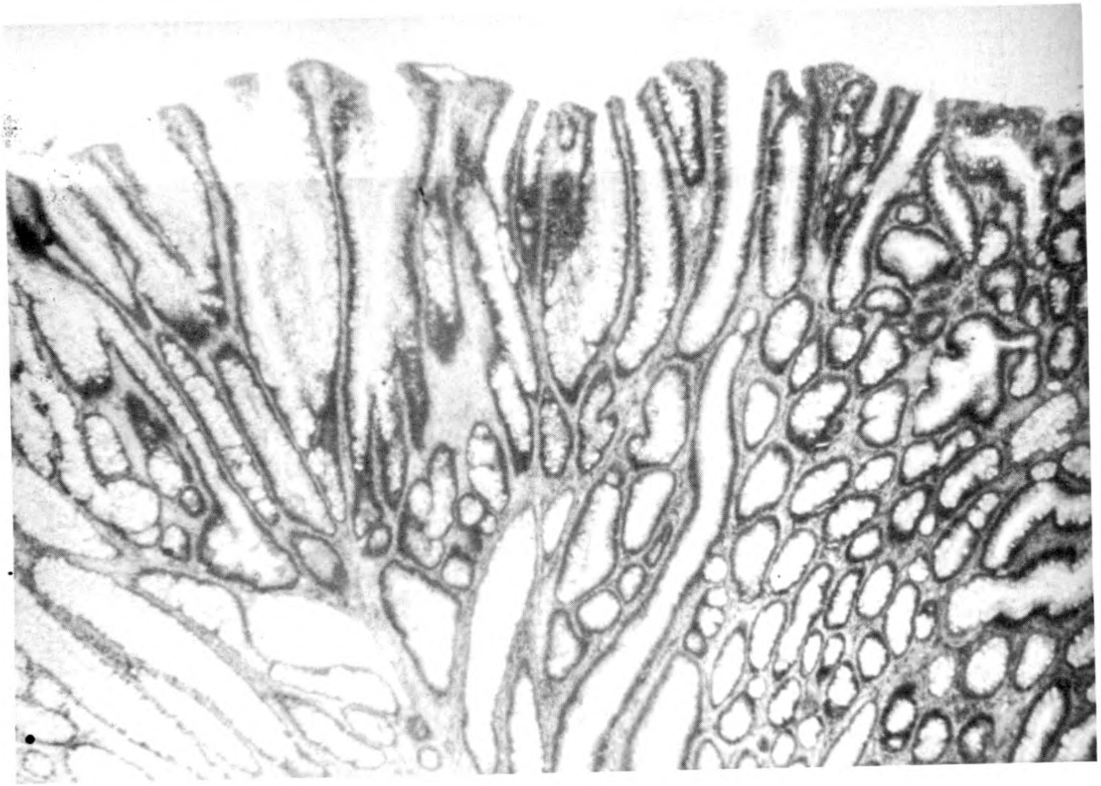


FIG. 5. Photomicrograph showing villous and adenomatous mucosal features in contiguous areas.

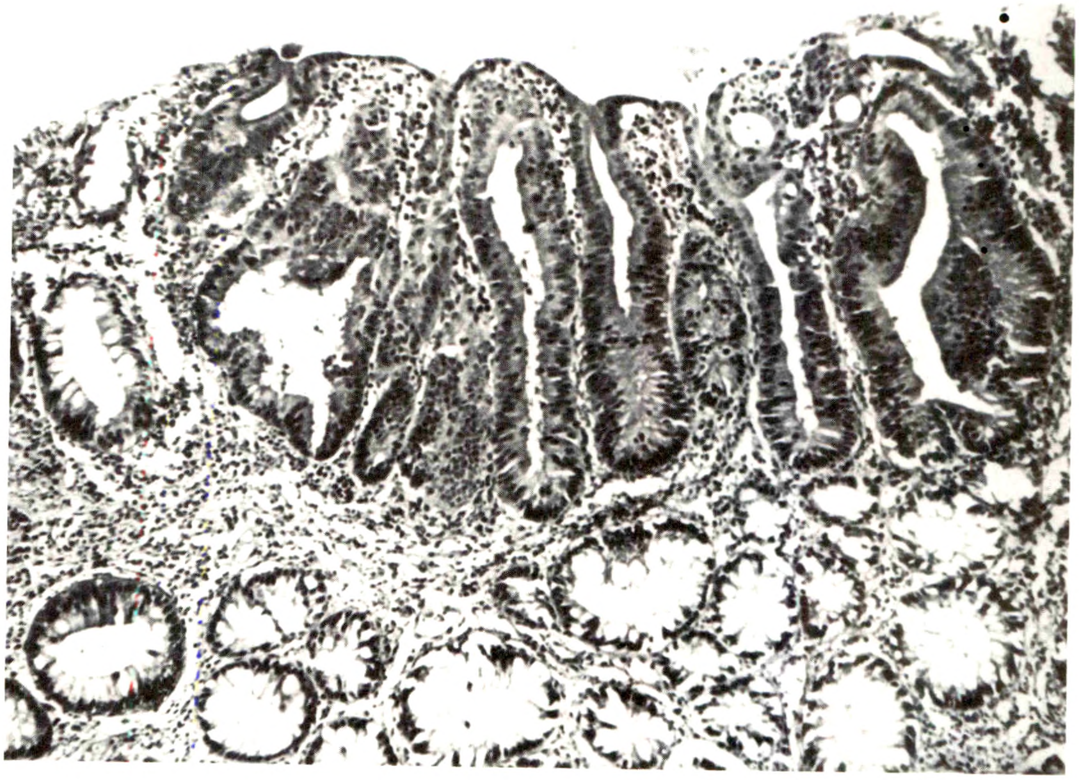


FIG. 6. Photomicrograph showing "focal atypia" in the mucous membrane of an adenomatous polyp.

i.e. at least through the muscularis mucosae, can be indisputably demonstrated (taking cognizance of artefactual errors) should the lesion be regarded as "clinically" malignant and we have so classified our material. Polypoid lesions in which it is not possible to demonstrate any remnant of a pre-existing adenomatous or villous polyp are termed "polypoid carcinomas". Obviously, there is a clear call for close collaboration between surgeon and

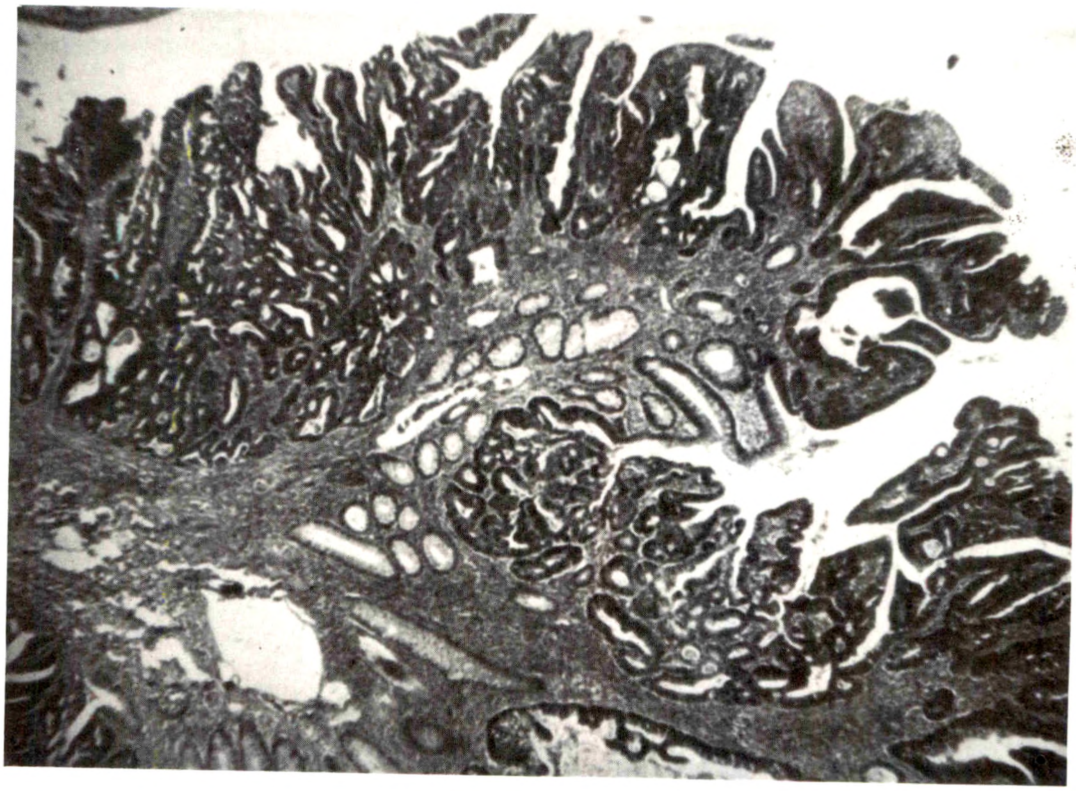


FIG. 7. Photomicrograph showing "superficial cancer" (Adenocarcinoma) in a polyp. This "cancer" does not extend beneath the muscularis mucosae.

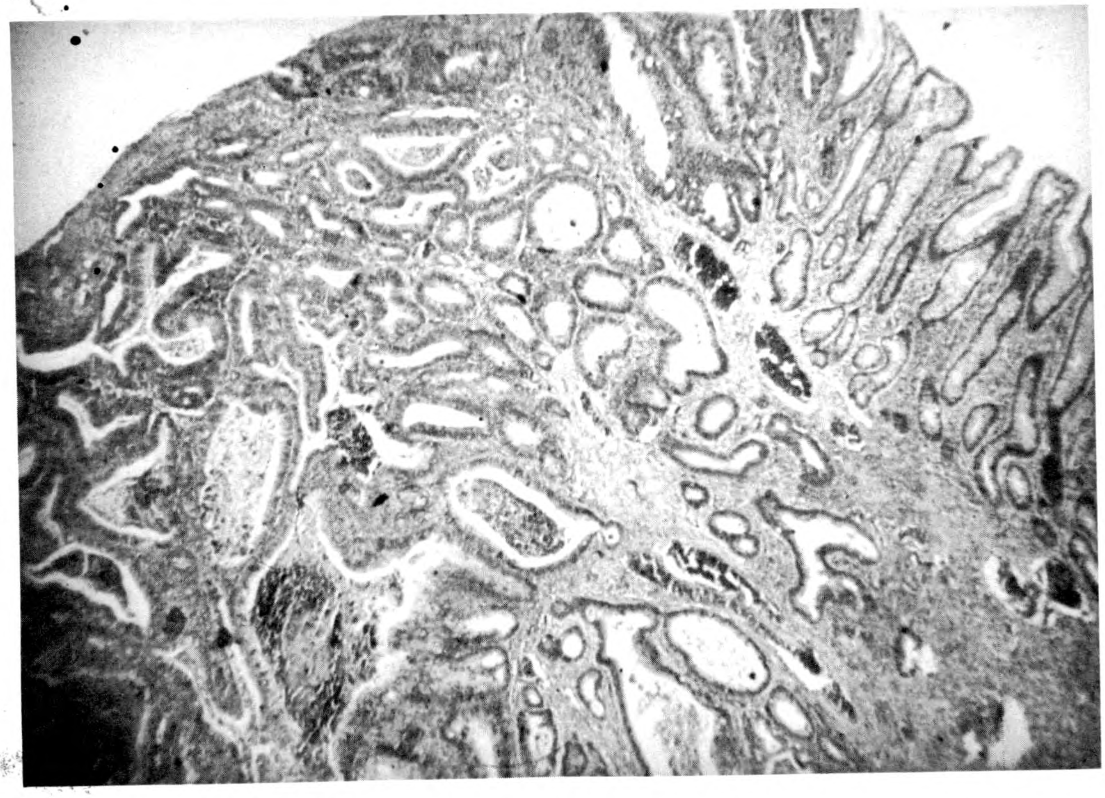


FIG. 8. Photomicrograph showing transition from normal mucosa (on right) to atypical glands formation (on left).

pathologist before final decisions with respect to management are made in these cases.

Parenthetically, one, not inconsiderable advantage of endoscopic removal is that the specimen may be considered as almost total biopsy, study of which can be carried out by the pathologist in complete and unhurried fashion without mutilation. Eventually, even this may prove to have limited value since there are indications

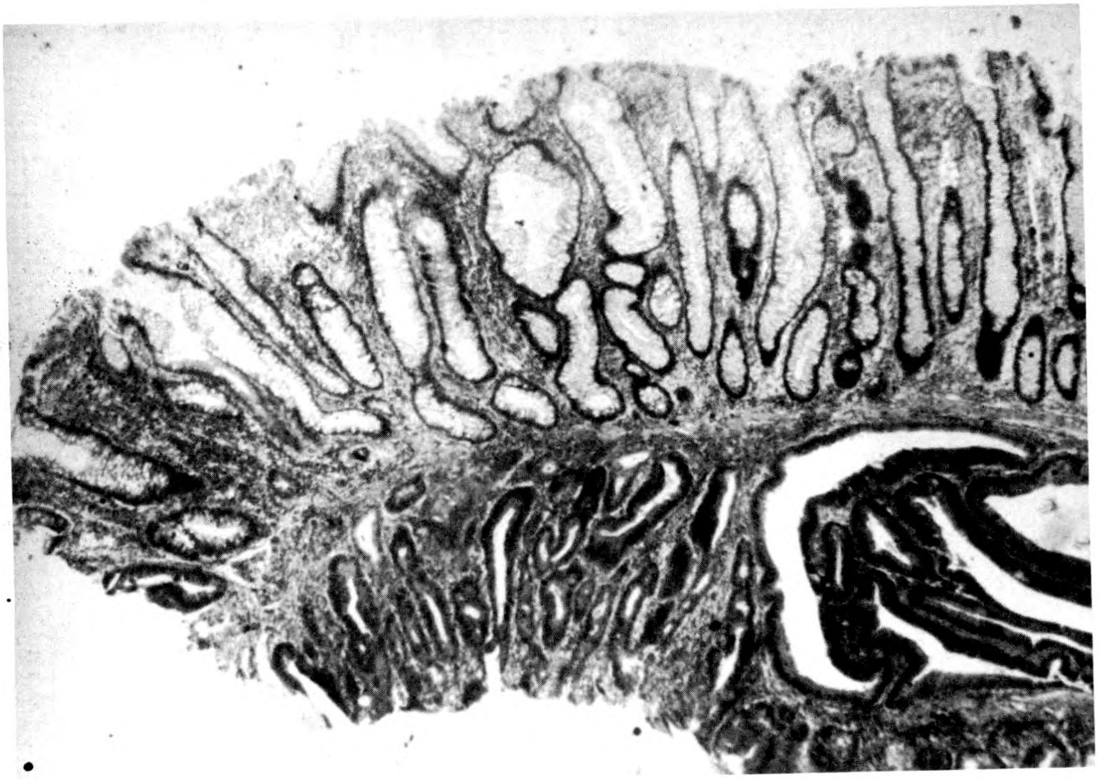


FIG. 9. Photomicrograph showing frank invasive adenocarcinoma extending beneath normal mucosa. (Same polyp as Fig. 6)

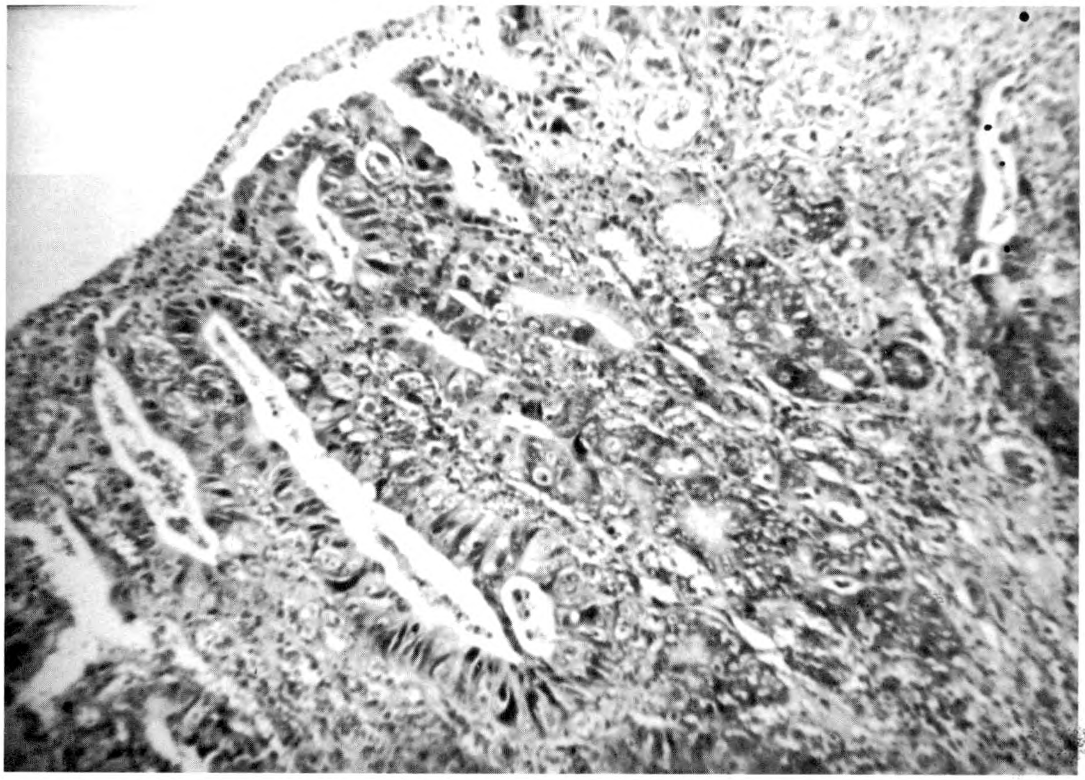


FIG. 10. Photomicrograph of frank invasive adenocarcinoma in an adenomatous polyp endoscopically removed (same polyp as Fig. 8).

that morphological criteria alone may not provide the final answer to the problem of malignant transformation.[3]

Management of "Malignant" Polyps

We encountered 17 such "malignant" polyps, or 3.4% of the total group. The findings and management of these are of interest. Only 16 patients were involved since one patient had two malignant polyps removed 2 months apart. In this patient and two others, it was deemed that endoscopic resection accomplished complete removal. These three patients had no further operation and have had no evidence of recurrence on endoscopic follow-up.

In 13 individuals abdominal intervention was deemed advisable based on the pathologic and endoscopic findings. Incidentally, two in this group came to us with a history of previous colonic resections for cancer. Such metachronous cancer is not too unexpected (*vide infra*).[3]

In 12 of these 13 patients, bowel resections were performed; in the remaining case no resection was performed because the surgeon could find no residual lesion, a fact confirmed by follow-up endoscopy.

Among the 12 colons resected, seven showed no residual tumor in the specimen. In five residual tumor was present. The only patient with lymph node metastases fell in the last group and this man had, in addition to a malignant polyp, an endoscopically recognized and biopsied adjacent small ulcerating adenocarcinoma.

We have found colonoscopy to be a very effective means of follow-up of patients with endoscopically resected lesions with respect to healing, persistence or recurrence. It is also the most favorable means of detection of additional polyps to which the polypectomized patient is particularly prone.[2,17,18,20,25]

A few words of caution are in order. Endoscopic polypectomy should not be undertaken until considerable expertise with the colonoscope has been achieved.[34,37,38] The full spectrum of surgical back-up in the event of complications should be available. Equally

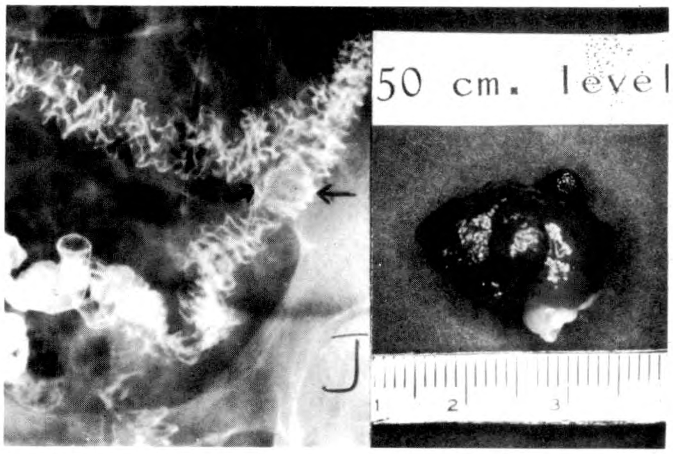


FIG. 11A. J.P. Barium enema X-ray performed on 67-year-old man with history of rectal bleeding and negative sigmoidoscopy. Villous adenoma shown was removed endoscopically.

important is the matter of not overlooking an early cancer while attention is focused on the polyp and its removal. We have encountered a number of such incidences. (Figs. 11 & 13) The increased incidence of cancer with polyps is well-documented[9,16,22,26,37] (Figs. 12 & 14).

In the literature, satellite polyps have been reported in association with 25% to 50% of colon carcinomas.[12,14,28,31] Also, it has been stated that the patient with multiple polyps is twice as likely to develop a colon cancer as the patient with a single polyp.[24] Morson[20] claims that of patients who have had a colon resection for cancer those whose specimens showed polyps in addition to the cancer have twice the chance of developing another, metachronous colonic neoplasm. Certainly, enlightened clinical practice embraces the concept that where a polyp is found, a careful search should be made for a colonic cancer as well.[10,23,29]

Conclusions

1. The fiberoptic colonoscope renders all parts of the colon endoscopically accessible in most patients.
2. Most polyps of the colon can be removed via the colonoscope once the requisite expertise has been realized.
3. Endoscopic polypectomy can be accomplished with a high degree of safety: 499 polyp removals are reported with no mortality and with only two significant complications.
4. Pedunculated polyps are more readily resected than sessile types but the latter are less frequent (9.4%). There may be a relationship between gross morphology, anatomical location and histologic classification.
5. Histologically, polyps may display mixed adenomatous and villous features in the mucosa more frequently than is generally appreciated.
6. Definite malignant changes were observed in 6.8% of polyps. However, clinically significant malignant change, manifested histopathologically as "invasive" cancer, was present in only 3.4%.
7. Endoscopic polypectomy can be regarded as almost total biopsy and permits complete and unhurried pathologic study of the entire lesion.
8. Selected "malignant" polyps may not require any more than endoscopic removal.
9. Endoscopic excision of colonic polyps should be undertaken only by those who have acquired proficiency in the use of the instruments and then only under circumstances favorable for management of potential complications.
10. The frequent association of separate colonic cancer with polyp formation should be recognized and pursuit of the polyp not permitted to obscure early diagnosis of an associated cancer.

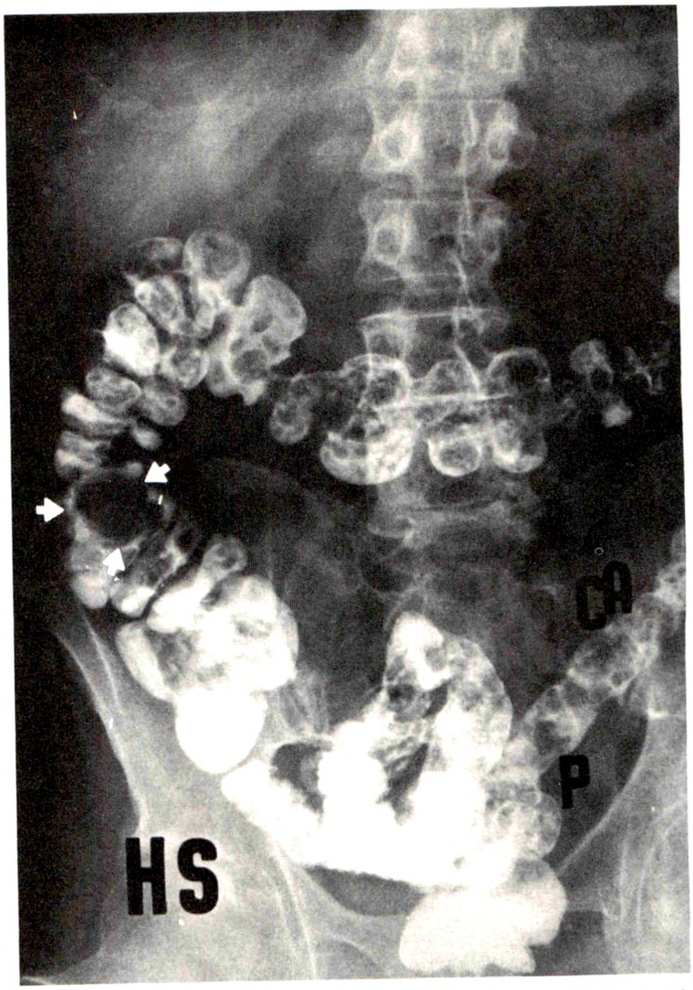


FIG. 12. H.S. Barium enema radiograph of a 49-year-old man with history of passing blood per rectum. Radiologic interpretation: polypoid neoplasm of ascending colon.

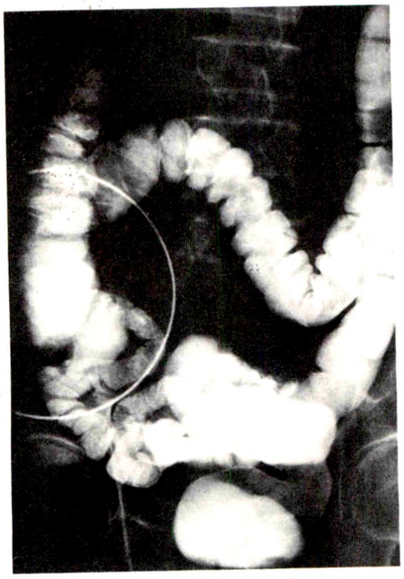
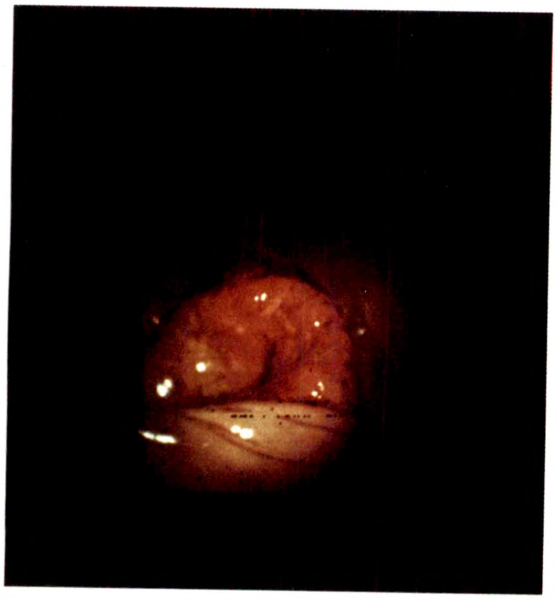
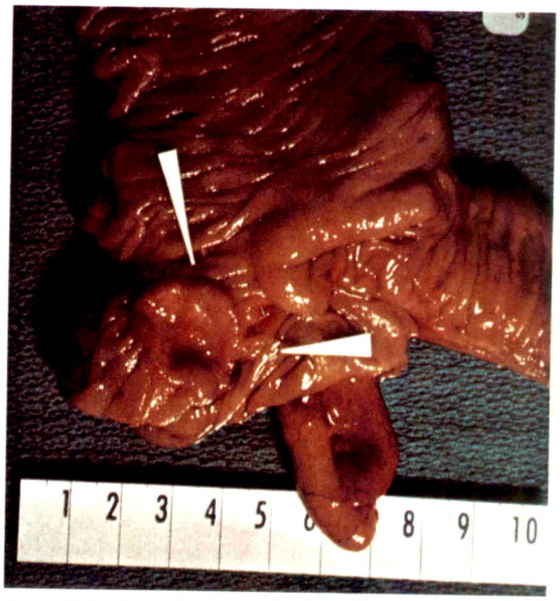
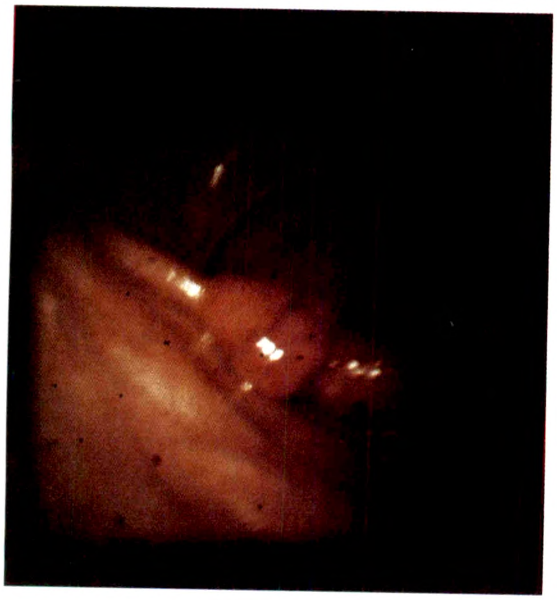
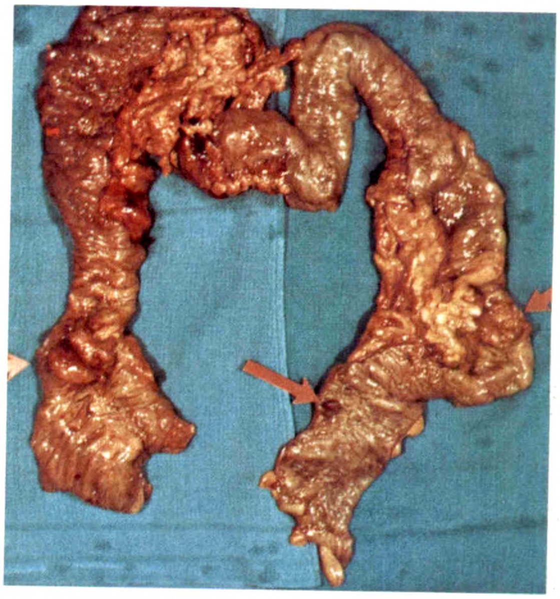


FIG. 11B. Repeat barium enema X-ray performed because of vague complaints. Interpretation:? abnormality of cecum.









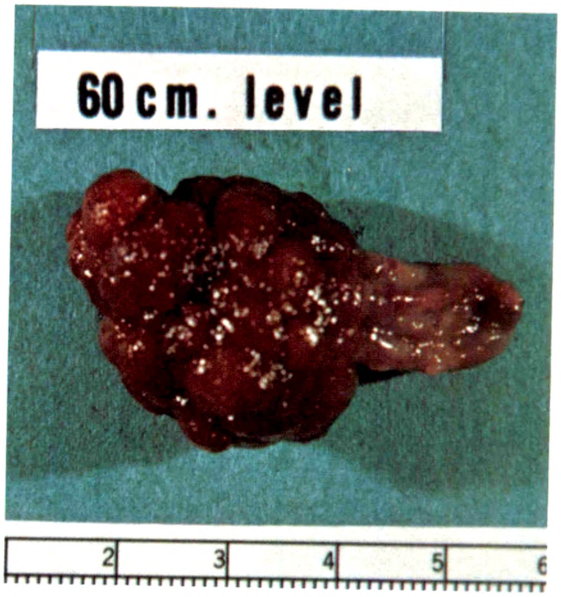


FIG. 13A (top left). Endoscopic view showing adenocarcinoma of cecum. (J.P. Fig. 11)

FIG. 13B (top right). Surgical specimen. (J.P. Fig. 11)

FIG. 14A (center left). Endoscopic view of radiologically undiagnosed polyp in sigmoid colon. (Beyond this was a small adenocarcinoma, also radiologically undiagnosed.) (H.S. Fig. 12)

FIG. 14B (center right). Surgical specimen following subtotal colectomy, showing carcinomas in ascending colon and sigmoid colon, as well as the polyp previously noted. (H.S. Fig. 12)

FIG. 15 (lower right). Five centimeter colonic polyp removed from descending colon (60 cm. level).

(Color photography financed by the Olympus Corporation of America)

References

1. Bloom, B. S., Goldhaber, S. Z., Sugarbaker, P. H. and O'Connor, N. E. Editorial. Fiberoptics: Morbidity and Cost. N. Engl. J. Med., 288:368, 1973.
2. Bockus, H. L., Tachdjian, V., Ferguson, L. K., Mouhran, Y. and Chamberlain, C.: Adenomatous Polyp of the Colon and Rectum: Its Relation to Carcinoma. Gastroenterology, 41:227, 1961.
3. Burdette, W. J.: Identification of Antecedents to Colorectal Cancer. Cancer, 28:51, 1971.
4. Castleman, B. and Krickstein, H.: Do Adenomatous Polyps of the Colon Become Malignant? N. Engl. J. Med., 267:469, 1962.
5. Castleman, B. and Krickstein, H.: Polyps of the Colon. Surg. Gynecol. Obstet., 116:752, 1963.
6. Enterline, H. T., Evan, G. W., Mercado-Lugo, R., Miller, L. and Fitts, W. Jr.: Malignant Potential of Adenomas of the Colon and Rectum. J. Am. Med. Assoc., 179:322, 1962.
7. Fisher, E. R. and Turnbull, R. B.: Malignant Polyps of the Rectum and Sigmoid: Therapy Based Upon Pathologic Considerations. Surg. Gynecol. Obstet., 94:619, 1952.
8. Fung, C. H. K. and Goldman, H.: The Incidence and Significance of Villous Change in Adenomatous Polyps. Am. J. Clin. Pathol., 53:21, 1970.
9. Ferraro, L. and Ross, S.: Evaluation of Villous Patterns in Tumors of the Colon and Rectum. Dis Colon Rectum, 8:144, 1965.
10. Grinnell, R. S.: The Rationale of Subtotal and Total Colectomy in the Treatment of Cancer and Multiple Polyps of the Colon. Surg. Gynecol. Obstet., 106:288, 1958.
11. Grinnell, R. S. and Lane, N.: Benign and Malignant Adenomatous Polyps and Papillary Adenomas of the Colon and Rectum. An Analysis of 1856 Tumors in 1335 Patients. Surg. Gynecol. Obstet. Internat. Abstr. Surg., 106:519, 1958.
12. Grosberg, S. J. and Galambos, J.: The Relationship of Polyps to the Survival of Patients Operated on for Carcinoma of the Large Bowel. Gastroenterology, 44:33, 1963.
13. Hedberg, S.: Quoted by Welch, 1973.
14. Helwig, E. B.: Adenomas and the Pathogenesis of Cancer of the Colon and Rectum. Dis. Colon Rectum, 2:5, 1959.
15. Hultborn, K. A.: The Causal Relationship Between Benign Epithelial Tumors and Adenocarcinoma of the Colon and Rectum. Acta Radiologica Supp., 113:1, 1954.
16. Jackman, R. J. and Beahrs, O. H.: Tumors of the Large Bowel. W. B. Saunders and Co., Philadelphia, 1968.
17. Judd, E. S. and Carisle, J. C.: Polyps of the Colon: Late Results of Transcolonic Removal. Arch. Surg., 67:353, 1953.
18. Kapp, D. F. and Quintero, J.: Quoted by Jackman and Beahrs.
19. Klein, R. R. and Scarborough, R. A.: Diagnosis and Treatment of Adenomatous Polyps of Colon. AMA Arch. Surg., 65:65, 1952.
20. Morson, B. C.: Control and Prevention of Intestinal Cancer. Brit. J. Hosp. Med., 1839, Nov. 1969.
21. Morson, B. C.: Precancerous and Early Malignant Lesions of the Large Intestine. Brit. J. Surg., 55:48, 1968.
22. Morson, B. C. and Bussey, H. J. R.: Predisposing Causes of Intestinal Cancer. Curr. Probl. Surg. Year Book Medical Publishers, Inc. Chicago, 1970.
23. Peabody, C. N. and Smithwick, R. H.: Practical Implications of Multiple Tumors of Colon and Rectum. N. Engl. J. Med., 264:853, 1961.
24. Rider, J. A., Kirsner, J. B., Moeller, H. C. and Palmer, W. L.: Polyps of the Colon and Rectum. A 4-year to 9-year follow-up study of 537 patients. JAMA, 170:638, 1959.
25. Rider, J. A., Kirsner, J. B., and Moeller, H. C. and Palmer, W. L.: Polyps of the Colon and Rectum: Their Incidence and Relationship to Carcinoma. Am. J. Med., 16:555, 1954.
26. Spratt, J. S., Ackerman, L. V. and Moyer, C. A.: Relationship of Polyps of the Colon to Colonic Cancer. Ann. Surg. 148:682, 1958.
27. Sugarbaker, P.: Quoted by Welch, 1973.
28. Swinton, N. and Weakley, F.: The Early Diagnosis of Carcinoma of the Colon and Rectum. Lahey Clin. Found. Bull., 12:227, 1962.
29. Turell, R. and Haller, J. D.: A Re-evaluation of the Malignant Potential of Colorectal Adenomas. Surg. Gynecol. Obstet., 119:867, 1964.
30. Welch, Claude E.: Medical Progress: Abdominal Surgery (Part II). N. Engl. J. Med., 288:661, 1973.
31. Welch, Claude E.: Polypoid Lesions of the Gastrointestinal Tract. W. B. Saunders Co. Philadelphia, 1964.
32. Welch, Claude E.: The Management of Polypoid Diseases. Cancer, 28:145, 1971.
33. Wolff, W. I.: Editorial. Colonoscopy and Endoscopic Polypectomy. N.Y. State J. Med., 73:641, 1973.
34. Wolff, W. I. and Shinya, H.: A New Approach to the Management of Colonic Polyps. Adv. Surg., Vol. 7, Chapter 2, Year Book Medical Publishers, Chicago 1973.
35. Wolff, W. I. and Shinya, H.: Colonfiberoscopy. J. Am. Med. Assoc., 217:1509, 1971.
36. Wolff, W. I. and Shinya, H.: Colonofiberoscopy: Diagnostic Modality and Therapeutic Application. Bull. Soc. Internat. Chir., 5:525, 1971.
37. Wolff, W. I. and Shinya, H.: Colonofiberscopic Management of Colonic Polyps. Dis. Colon Rectum, 16:87, 1973.
38. Wolff, W. I. and Shinya, H.: Polypectomy via the Fiberoptic Colonoscope. N. Engl. J. Med., 288:329, 1973.
39. Wolff, W. I., Shinya, H., Geffen, A. and Ozoktay, S. I.: Colonofiberoscopy. Am. J. Surg., 123:180, 1972.

DISCUSSION

DR. MOSES J. FOLKMAN (Boston): I enjoyed Dr. Wolff's paper and would add that the colonscope is also useful in children.

Two weeks ago I had to operate on a 9-year-old girl who was bleeding steadily from multiple vascular malformations in the lumen of the small bowel. She had had three previous laparotomies and multiple blind small bowel resections had to be done because these malformations could not be seen from the serosa.

The Children's Hospital does not have a colonoscope but the Brigham has one and these two institutions are fortunately hooked together by a single bridge. Dr. Sugarbaker from Dr. Moore's department brought over their colonoscope and we used it in the operating room.

Before draping the patient, we inserted it into the rectum and performed a laparotomy. We were able to pass the colonoscope through the entire bowel by threading the bowel over it all the way to the duodenal-jejunal junction. We turned out the lights in the operating room and by turning up the light in the scope we could see through the bowel wall at every point and spot the malformations which were confirmed by the colonoscopist looking in the lumen. You can see the scope here passing through the colon.

We were able to resect the two large malformations, one in the jejunum and one in the ileum. The colonoscope was also helpful at the end of the procedure because the bowel was very dilated with air but the scope was passed up to the duodenum, suction on the scope was turned on, the scope was pulled back through the bowel. The bowel collapsed and the abdomen was easily closed.

Dr. Claude E. Welch (Boston): We are all very grateful to Drs. Wolff and Shinya for their contributions to this rapidly expanding field and also for their great generosity in demonstrating their technics to so many people.

Among others from our institution, Dr. Steven Hedberg sat at their feet for a few days and has developed the procedure at the Massachusetts General Hospital. If I may be permitted to show a couple of slides, I would like to comment on some of the points that Dr. Wolff has made.

The first slide illustrates the fact that 123 polyps were removed up to the 31st of March, 1973. In this group 11 polypoid lesions were found to contain cancer. In this group the villous adenomas were by far the most dangerous. On the other hand, there was one adenomatous polyp that contained a cancer. The villoglandular polyps in this small series showed no concurrent cancer though we have observed it in other series. Polypoid carcinomas were found in 4 of the 11. Our figures agree rather closely with those of Dr. Wolff, namely that the cancer is present in about 8 to 10% in all of the lesions that are removed.

In contradistinction to his findings, however, we have not found colonoscopy-polypectomy quite as safe a procedure. One patient bled severely during a diagnostic colonoscopy because of rupture of the spleen. Three others have had rather severe bleeding. Two have had perforations. The patient with the ruptured spleen and the two with the perforations required laparotomy while the other complications were treated in a conservative fashion.

Our figures also show that there are many polyps, some of which are as large as 2 centimeters in diameter that are discovered by this method which have not been detected by the barium enema.

There certainly is no question but that this method of diagnosis and treatment is extremely valuable. In another year or two the whole history of polyps and of early cancer of the colon will undergo important revisions because of the data that will be obtained. Meanwhile, there is certainly no question but that we must take a careful look at the method by which polypectomy, in particular is being effected.

Dr. John Englebert Dunphy (San Francisco): I should like to congratulate Dr. Wolff and also thank him for a major contribution to colonic surgery.

Dr. Theodore Schrock from our department spent a substantial period of time with Dr. Wolff. Upon his return, he performed 100 colonoscopies before attempting a polypectomy. He has performed about 300 colonoscopies. He has removed polyps from 70 odd patients.

There have been essentially no complications, except one bleeding episode following morcellation of a very large polyp.

In addition to its role in colonoscopy—or rather in the management of polyps, it has been of extreme value in the detection of some early carcinomas where the X-ray was either negative or vaguely suspicious. A definitive diagnosis has been possible instead of repeating the barium enema in several months time. Finally, it has been very helpful in the appraisal of patients with a variety of stages of Crohn's disease, particularly in a lesion which appeared to be apparently segmental colitis but on colonoscopy was, in fact, total.

I am certain if one is to remove polyps with this instrument this is indeed a surgical procedure. The use of the instrument should be concentrated in the hands of a few members of the staff who are quite willing to devote the time and acquire the expertise and skill to do it safely and well. I believe this instrument is going to essentially eliminate the need for abdominal laparotomy in the control of polyps.

Dr. Francis D. Moore (Boston): I also would like to congratulate Dr. Wolff and Dr. Shinya in what I think is a quantum advance in abdominal surgery in this past couple of years.

We felt we should not get involved in this without careful study. In February 1971 Dr. Wolff and Dr. Shinya were kind enough to welcome one of our residents, Dr. Paul Sugarbaker, to study with them. I am sorry he can not be here today to speak. Since that time, we have done 355 colonoscopies of which 109 polyps have been removed.

Although many of the colonoscopies of a diagnostic type have been ambulatory, all of the polypectomies have been done in the hospital, in hospitalized patients. All were done in the operating room and the patient had operative preparation. The anesthetist had known that the procedure was going on even though no anesthesia was used because we realized that we may have undesirable complications.

Of these 109 polyps most were 0.5–3.0 cm. in diameter. Four others were so large and so broad based that they were deferred and treated by open laparotomy.

The per cent proved to be carcinoma and a half of them were invasive.

It is disappointing that of all of the patients with polyps who had preoperative measurement of their carcinomoembryionic antigen, none have had positive assays even though the polyp was malignant.

We have had three complications, one bleeding requiring operation and two free perforations. Dr. Wolff mentioned an interesting thing: the asymptomatic perforation. This colon is filled with air and when it perforates it does not give the patient a very acute abdomen. We must have a very high index of suspicion and if necessary, of course, check it by X-ray.

Our group has been interested by the fact that if there is sharp pain whatsoever at the time the polyp is removed by cauterization, beware, this suggests that the visceral peritoneum is being irritated by the cautery.

Confirming what Dr. Dunphy has said, we have had 14 patients in whom the x-ray department would not make a flat-footed diagnosis of diverticulitis versus carcinoma (or both), and the colonoscopy has called it correctly in all cases.

I feel this method of colonoscopy is going to be widely used. I think it is a fairly hazardous procedure. I think it also requires a lot of time. Many of us are used to doing a quick proctoscopy or sigmoidoscopy. Many of these colonoscopy examinations take 1½ or 2 hours. I believe there should be very careful training or apprenticeship with an expert before a person undertakes this procedure, so as to reduce the hazard.

Dr. William I. Wolff (Closing): I would like to thank all the discussants for their very kind remarks.

I want to congratulate Dr. Folkman on his bold and imaginative intra-operative use of the endoscope.

Dr. Welch's monograph on this subject has been of inestimable value to us. One of the confusing features in the pathology of these types of polyps is in the group which Dr. Welch calls "villoglandular." Unfortunately, Dr. Morson, the British pathologist, refers to these as "papillary adenomas" and in this country we use the term "papillary" as synonymous with "villous" adenoma.

I agree with Dr. Dunphy's comments that this is not something that should be turned over to somebody and anybody. We think one or two members of a given staff should spend time with it and develop the requisite expertise. I am hopeful that surgeons will get into this program before the gastroenterologists take it over completely.

I agree with Dr. Moore's comments. Time did not permit the fact to be brought out that we do hospitalize all our patients who are candidates for polypectomy. They are very carefully worked up, with the idea in mind that should a complication occur, we can move rapidly into the operating room to treat the patient, if necessary. Close follow-up of these patients is mandatory.

These patients have to be seen by someone a number of hours after the procedure is done, even though it had seemed to be a very safe procedure. Proper preparation means that the bowel is well cleaned out. The clinical signs and findings may be minimal then, should a small perforation occur.

The determination of carcinoembryonic antigen levels is a very interesting subject and one which we are beginning to pursue with the help of Dr. Zamcheck. It is hoped that by getting specimens on these patients; when the tests for CEA become more sensitive, we might be able to find something interesting with this examination. It is possible that even at the present time this determination does have a use and I would say that a patient who has a polyp and has an elevated CEA antigen, should have a careful search made for an associated carcinoma.

I would really like to emphasize a point that associated carcinomas may be missed if they are not kept in mind and, if I may, I would just show four slides here which will very briefly demonstrate this point.

This is a patient with a 10-year history of spastic colitis who had some rectal bleeding. He was sigmoidoscoped. Nothing was found. He had a barium enema X-ray and a polyp was found in his sigmoid colon (Fig. 11a).

This was removed endoscopically (Fig. 11A). The patient came in later with some rather vague complaints. I do not know why but I looked over his barium enema and I thought the cecum didn't look exactly perfect (Fig. 11B).

We did a repeat colonoscopy after finding guaiac positive stools and went all the way around to the cecum and found a very early carcinoma in the cecum (Fig. 13A).

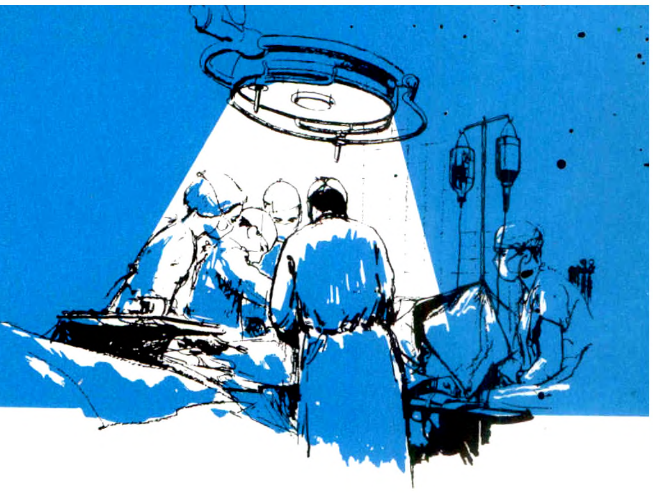
This slide is the barium enema X-ray done after a negative sigmoidoscopy after the bleeding episode. This is the polyp, seen endoscopically at the 50 cm. level, which was removed.

This is the repeat barium enema X-ray showing a questionable cecal lesion. On review by the radiologists they were unable to make any definite diagnosis. They said there might be some retained fecal material in there. We decided under the circumstances to colonoscope the patient. The tip of the colonoscope is now in the cecum, as seen here and this is the lesion in question (Fig. 13A).

Here is the surgical specimen, the appendix here, and here showing early carcinoma in the cecum itself (Fig. 13B).

I think that as more people become involved in this procedure they are going to be so intent in removing the polyp that they are going to overlook the possibility of an associated carcinoma.

What's your surgical I.Q.?



☐ **Up to date?** ☐ **Don't know?**

If you answered "up-to-date" you can double check on yourself with a SESAP assessment. If you answered "don't know" you can turn to SESAP as a reliable way of determining how current your surgical knowledge really is . . . and learn of the specific areas where you need more up-to-date information.

WHAT SESAP IS:
SESAP is the Surgical Education and Self-Assessment Program of the American College of Surgeons. It's a simple method to help a surgeon evaluate his own knowledge in areas essential to his practice. It suggests new information vital to his self-education.

UP TO DATE:
Truly a program of continuing education, SESAP will be revised every three years to offer you new knowledge as it becomes tested and accepted in surgical practice. The current program will be succeeded in October 1974 by SESAP II.

FOR ALL SURGEONS:
SESAP covers that body of knowledge which should be possessed by general surgeons and specialists alike. It is available to all doctors of medicine, including residents.

INDIVIDUALIZED:
With SESAP, you can identify those areas in which you may be strong or deficient; design an educational program matching your own needs, and compare your surgical knowledge with the knowledge of your peers.

COMPREHENSIVE:
SESAP covers 750 items in nine areas essential to your daily practice.

CLINICAL:
SESAP stresses problems of patient management, x-ray interpretation, recognition of pathologic conditions, and important physiologic principles underlying the care of the surgical patient.

THOROUGHLY REFERENCED:
Each item is indexed in an extensive bibliography, including both standard textbooks and the current surgical literature.

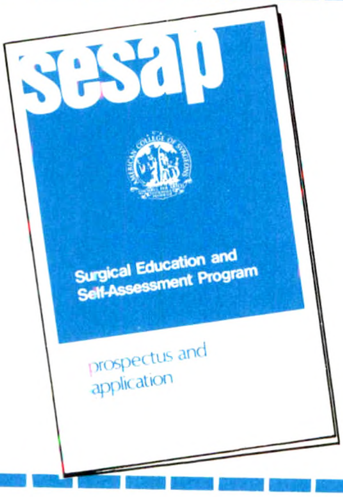
CONVENIENT:
You may complete SESAP at any time, anywhere—in your own home or office, while traveling, or while on vacation. You set your own learning pace.

CONFIDENTIAL:
Only you will ever know your performance. Nothing will be returned to the American College of Surgeons or any other agency.

LEARN HOW YOU CAN EVALUATE YOUR SURGICAL KNOWLEDGE in the privacy of your office and home . . . send for free Prospectus today.

SESAP American College of Surgeons

55 EAST ERIE STREET
CHICAGO, ILLINOIS 60611


sesap
Surgical Education and Self-Assessment Program
prospectus and application

Complete details with application for SESAP. Send for copy. No obligation.

YES, I wish to keep myself informed about current surgical knowledge. Please send me, without obligation, a Prospectus explaining the Surgical Education and Self-Assessment Program of the American College of Surgeons.

Name ______________________ M.D.

Address ______________________

City & State ______________ Zip ______

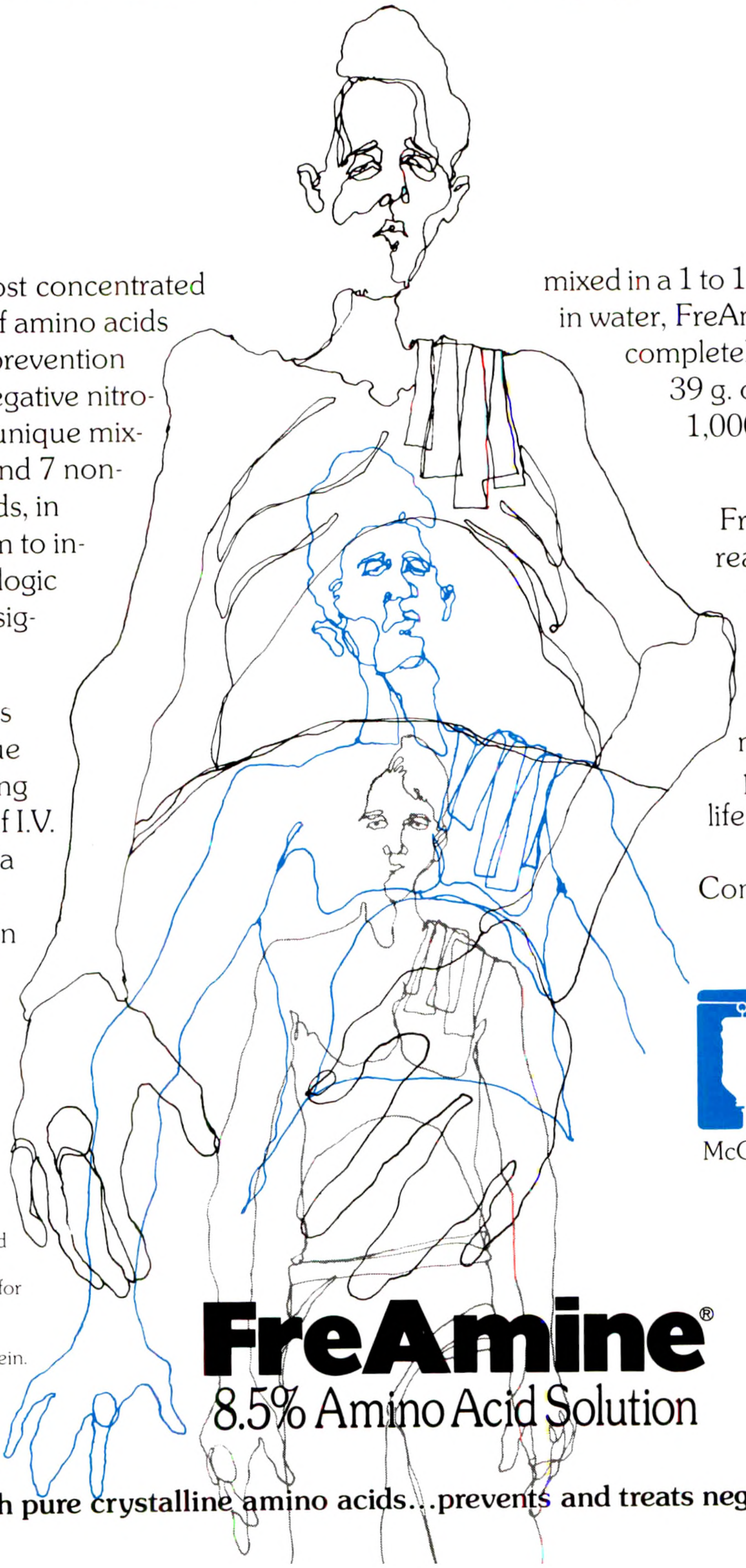
AS 9/73

When life hangs on protein intake… FreAmine® is life-supportive.*

FreAmine is the most concentrated parenteral source of amino acids obtainable for the prevention and treatment of negative nitrogen balance. It is a unique mixture of 8 essential and 7 nonessential amino acids, in pure crystalline form to insure immediate biologic availability without significant waste.

FreAmine promotes anabolism and tissue synthesis even during extended periods of I.V. nutrition. Its formula is based on the two international protein standards. When mixed in a 1 to 1 ratio with 50% dextrose in water, FreAmine provides 6.25 g. of completely utilizable nitrogen and 39 g. of protein equivalent per 1,000 ml, plus 850 total nonprotein calories.

FreAmine is furnished in a ready-to-mix kit containing everything necessary for basic hyperalimentation, including 50% dextrose in water. Find out more about how McGaw puts it all together—with life-supporting I.V. nutrition in convenient kit form. Contact your McGaw representative or write for free brochure.



McGaw puts it all together.

FreAmine®

8.5% Amino Acid Solution

Supports life with pure crystalline amino acids…prevents and treats negative nitrogen balance.*

*With adequate calories and other nutrients, when oral alimentation is not feasible for prolonged periods and/or there is impaired gastro-intestinal absorption of protein.

DESCRIPTION: Each 100 ml. contains: FreAmine Amino Acid Mixture*, 8.5 g; Sodium Bisulfite, U.S.P., less than 0.10 g.; Water for Injection, U.S.P. q.s., pH adjusted with acetic acid (approximately 20 mEq./1. Acetate).

Approximate concentration of amino acids (g./100 ml.):

Essential Amino Acids: L-Isoleucine 0.59; L-Leucine 0.77; L-Lysine HCl 0.77; Methionine 0.45; L-Phenylalanine 0.48; L-Threonine 0.34; L-Tryptophan 0.13; L-Valine 0.56.

Nonessential Amino Acids: L-Alanine 0.60; L-Arginine 0.31; L-Histidine 0.24; L-Proline 0.95; L-Serine 0.50; Aminoacetic Acid (Glycine) 1.8; L-Cysteine • HCl • H_2O $<$0.02. Alpha amino nitrogen greater than 80% of total nitrogen present. Concentration of Electrolytes (mEq./1.): Sodium 10, Chloride 45.

8.5% FreAmine Solution is a sterile, nonpyrogenic solution containing pure crystalline amino acids. A 500 ml. unit provides a total of 39 g. of protein equivalent and 6.25 g. of nitrogen.

ACTIONS: 8.5% FreAmine Solution provides, in concentrated form, a physiological ratio of completely utilizable amino acids for protein synthesis. Used with concentrated carbohydrate solutions, e.g., 20 to 50% dextrose solutions, as a source of calories plus electrolytes and vitamins, it provides total parenteral nutrition.

INDICATIONS: As an adjunct in the prevention of nitrogen loss, or in the treatment of negative nitrogen balance in patients where: (1) oral alimentation is not feasible for prolonged periods, and (2) there is impaired gastrointestinal absorption of protein.

CONTRAINDICATIONS: 1. Anuria. 2. Hepatic coma.

WARNINGS: Administration of amino acids to a patient with hepatic or renal insufficiency may result in a rise in blood ammonia or urea nitrogen. Rare instances of typically asymptomatic hyperammonemia have been reported in patients with no evidence of liver dysfunction receiving total parenteral nutrition. Since it appears dose-related, and more likely to develop in infants on prolonged total parenteral nutrition, conservative doses of amino acids should be given and blood ammonia periodically measured. If symptomatic hyperammonemia should develop, the nitrogen-containing solution should be discontinued and the patient's clinical status reevaluated.

The safe use of FreAmine in pregnant women has not been demonstrated.

PRECAUTIONS: It is essential to provide adequate calories for utilization of amino acids.

Hypertonic nutrient solutions should be administered through an indwelling intravenous catheter with the tip located in the superior vena cava.

HYPERALIMENTATION COMPLICATIONS: Potentially dangerous complications can be minimized by adherence to a careful protocol by an experienced team of pharmacist, nurse, and physician.

To prevent sepsis, rigid aseptic technique must be used in solution preparation and catheter placement and care.

The catheter dressing should be aseptically changed every 2-4 days and whenever contamination is suspected.

Consult clinical literature for discussion of management of sepsis during hyperalimentation.

The following metabolic complications have been reported: metabolic acidosis, hypophosphatemia, alkalosis, hyperglycemia and glycosuria, osmotic diuresis and dehydration, rebound hypoglycemia, elevated liver enzymes, and electrolyte imbalances. Frequent clinical evaluation and laboratory determinations are necessary to prevent or minimize these complications.

ADVERSE REACTIONS: Rare instances of hyperammonemia (see Warnings), and minor local reactions consisting of a warm sensation and erythema when FreAmine and hypertonic dextrose were administered by peripheral vein, have been reported.

DOSAGE AND ADMINISTRATION: Recommended Dietary Allowances of protein are approximately 0.9 g. per kilogram of body weight for a healthy adult and 1.4 to 2.2 g. per kilogram for healthy growing infants and children.** Requirements in trauma or malnutrition may be substantially increased. During hyperalimentation daily doses of approximately 1.0 to 1.5 g. per kilogram of body weight for adults and 2 to 3 g. per kilogram of body weight for infants are generally sufficient.

Calorie-to-nitrogen ratios of at least 100 to 150 nonprotein calories per gram of nitrogen have been recommended and may be provided by concentrated dextrose.

Sufficient vitamins, electrolytes, principally potassium, magnesium, and phosphate, as well as sodium, calcium, and chloride, must be given. Calcium and phosphate may be added to alternate infusate bottles to avoid precipitation, and sodium and potassium added as acetate or lactate salts to provide bicarbonate precursor. Serum electrolytes must be monitored frequently.

In adults, hypertonic mixtures may be safely administered only by continuous infusion through a central venous catheter with the tip located in the vena cava. 500 ml. of 8.5% FreAmine Solution, appropriately mixed with dextrose, electrolytes, and vitamins, is typically administered over an eight-hour period. Administration rate is governed by protein requirements and glucose tolerance. Advance dosage slowly with frequent determination of urine and blood sugar levels.

To prevent rebound hypoglycemia, 5% dextrose should be administered when hypertonic dextrose infusions are abruptly discontinued.

PEDIATRIC DOSAGE AND ADMINISTRATION: Small infants (up to 10 kg.) on total parenteral nutrition generally receive 2 to 3 g. of protein, 100 calories, and 120 to 150 ml. of fluid per kg. of body weight per day, provided in a solution of approximately 2⅛% FreAmine in 20% dextrose. Advance dosage slowly with frequent monitoring. (See Warnings above)

Large infants and children generally require 50 to 80 calories per kg. per day.

ROUTE: Intravenous.

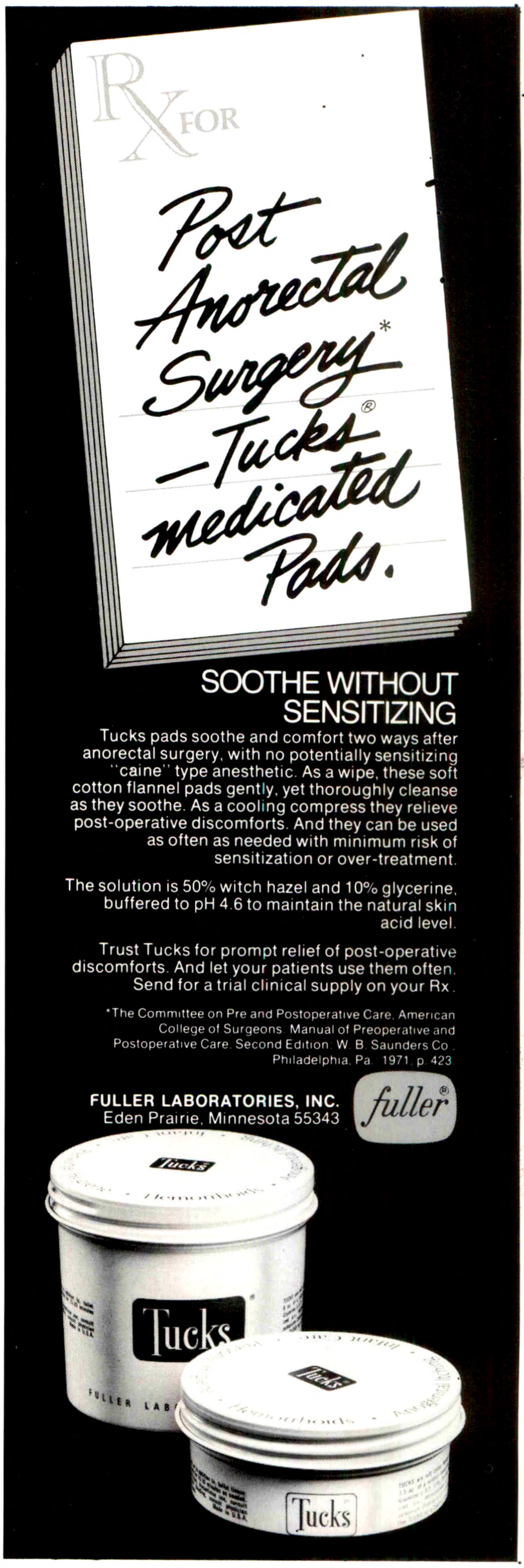
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

HOW SUPPLIED: 8.5% FreAmine Solution is supplied sterile and nonpyrogenic in 500 ml. intravenous infusion bottles.

*Crystalline amino acid mixture, isolated and purified from edible soybean hydrolysate or synthesized.

**500 ml. of 8.5% FreAmine Solution contains 6.25 g. of nitrogen, and the equivalent of 39 g. of protein.

McGAW LABORATORIES
Division of American Hospital Supply Corporation
Glendale, California • Milledgeville, Georgia



SOOTHE WITHOUT SENSITIZING

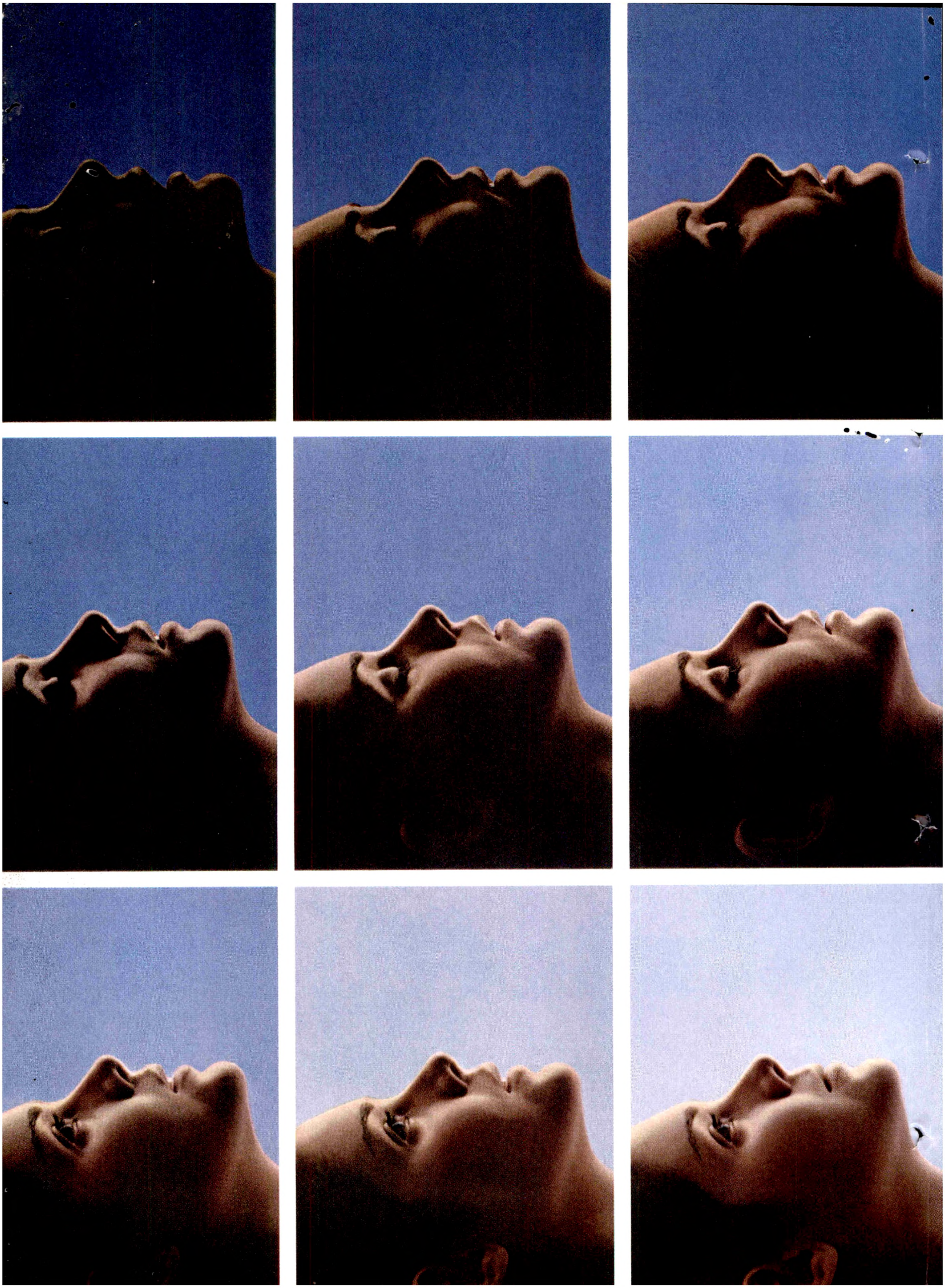
Tucks pads soothe and comfort two ways after anorectal surgery, with no potentially sensitizing "caine" type anesthetic. As a wipe, these soft cotton flannel pads gently, yet thoroughly cleanse as they soothe. As a cooling compress they relieve post-operative discomforts. And they can be used as often as needed with minimum risk of sensitization or over-treatment.

The solution is 50% witch hazel and 10% glycerine, buffered to pH 4.6 to maintain the natural skin acid level.

Trust Tucks for prompt relief of post-operative discomforts. And let your patients use them often. Send for a trial clinical supply on your Rx.

*The Committee on Pre and Postoperative Care, American College of Surgeons. Manual of Preoperative and Postoperative Care, Second Edition. W. B. Saunders Co., Philadelphia, Pa., 1971, p. 423.

FULLER LABORATORIES, INC.
Eden Prairie, Minnesota 55343



Three ways to minimize emergence reactions when you use Kētalar®

(Ketamine HCl)

Let's face it: nearly every anesthesiologist knows by now that Ketalar is an unusually effective general anesthetic or induction agent, with a wide margin of safety. Many view it, in fact, as a major advance in the treatment of such high-risk patients as the very young and the very old... burn cases... accident victims... and those suffering from respiratory disorders such as emphysema.

And nearly every anesthesiologist also knows from the literature (or his own personal experience) that some patients have experienced unpleasant emergence reactions following the administration of Ketalar.

What is perhaps less known is that a combination of patient selection, addition of certain drugs, and the lessening of external stimuli has proved effective in reducing the incidence and severity of emergence reactions. These techniques are easy to apply and, according to many clinical investigators, are remarkably useful.

1. Presurgical medication

High on the list of methods of reducing emergence reactions are certain drugs used preoperatively. These reactions can often be prevented by administering:

Droperidol, 0.1 mg/kg, IM,
30 minutes before anesthesia.

2. Postsurgical medication

After surgery, emergence reactions can often be aborted or prevented entirely by administering one of the following:

Droperidol, 0.07 to 0.1 mg/kg, IV
Diazepam, 0.1 to 0.3 mg/kg, IV
A subanesthetic dose of an ultrashort-acting barbiturate.

3. Avoid tactile and auditory stimuli whenever possible

The incidence of emergence reactions following Ketalar anesthesia appears to be profoundly affected by external auditory and tactile stimuli. Ideally, the patient should be engaged in calm, noncontroversial conversation (on a single subject, if possible) before surgery; afterward, he should be permitted to emerge from anesthesia with minimal auditory, visual, and tactile stimuli.

Will the three preventive techniques discussed here – patient selection, drugs, and ambience – obviate all emergence reactions following Ketalar anesthesia? No, but they will significantly reduce the incidence and severity of those reactions.

Any assessment of Ketalar, however, should take into account its many important advantages – especially for the high-risk patient, where efficacy and a wide margin of safety have made it increasingly valuable to today's anesthesiologists. As more and more are discovering every day.

See next page for prescribing information.

advancement in anesthesiology

Kētalar
(Ketamine HCl)
Parke-Davis

advancement in anesthesiology Ketalar®
(Ketamine HCl)

KETALAR (Ketamine Hydrochloride)

- **SPECIAL NOTE:** EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12 PER CENT OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT DREAM-LIKE STATES, VIVID IMAGERY; HALLUCINATIONS AND EMERGENCE DELIRIUM. IN SOME CASES THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY LASTS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR. THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY.

THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS. IN ADDITION, THE USE OF A SMALL HYPNOTIC-DOSE OF A SHORT-ACTING OR ULTRASHORT-ACTING BARBITURATE OR OTHER AGENT SUCH AS DIAZEPAM MAY BE REQUIRED TO TERMINATE A SEVERE EMERGENCE REACTION. CERTAIN DRUGS SUCH AS DROPERIDOL OR DIAZEPAM INTRAMUSCULARLY HAVE ALSO BEEN USED IN AN ATTEMPT TO REDUCE THE INCIDENCE OF EMERGENCE REACTIONS: SUFFICIENT DATA HAVE NOT YET BEEN ACCUMULATED TO CONSTITUTE THOROUGH DOCUMENTATION. THE INCIDENCE OF EMERGENCE REACTIONS IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

INDICATIONS: Ketalar is recommended: 1. as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketalar is best suited for short procedures but it can be used, with additional doses, for longer procedures. 2. for the induction of anesthesia prior to the administration of other general anesthetic agents. 3. to supplement low-potency agents, such as nitrous oxide.

See package insert for full prescribing information.

CONTRAINDICATIONS: Ketalar is contraindicated in persons in whom a significant elevation of blood pressure would constitute a serious hazard and those who have shown hypersensitivity to the drug.

WARNINGS: Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation. Barbiturates and Ketalar *should not* be injected from the same syringe. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar. Postoperative confusional states may occur during the recovery period. Respiratory depression may occur with over-dosage or too rapid a rate of administration of Ketalar in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

USAGE IN PREGNANCY: Since the safe use in pregnancy, including obstetrics, has not been established, such use is not recommended.

PRECAUTIONS: Because pharyngeal and laryngeal reflexes are usually active, Ketalar should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances. Resuscitative equipment should be ready for use. *The incidence of emergence reactions may be reduced* if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note). The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response. In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

ADVERSE REACTIONS: *Cardiovascular:* Blood pressure and pulse rate are frequently elevated following administration of Ketalar. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketalar. Laryngospasms and other forms of airway obstruction have occurred during Ketalar anesthesia.

Eye: Diplopia and nystagmus have been noted following Ketalar administration. It also may cause a slight elevation in intraocular pressure measurement.

Psychological: (See Special Note).

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures.

Gastrointestinal: Anorexia, nausea or vomiting have been observed; however this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness.

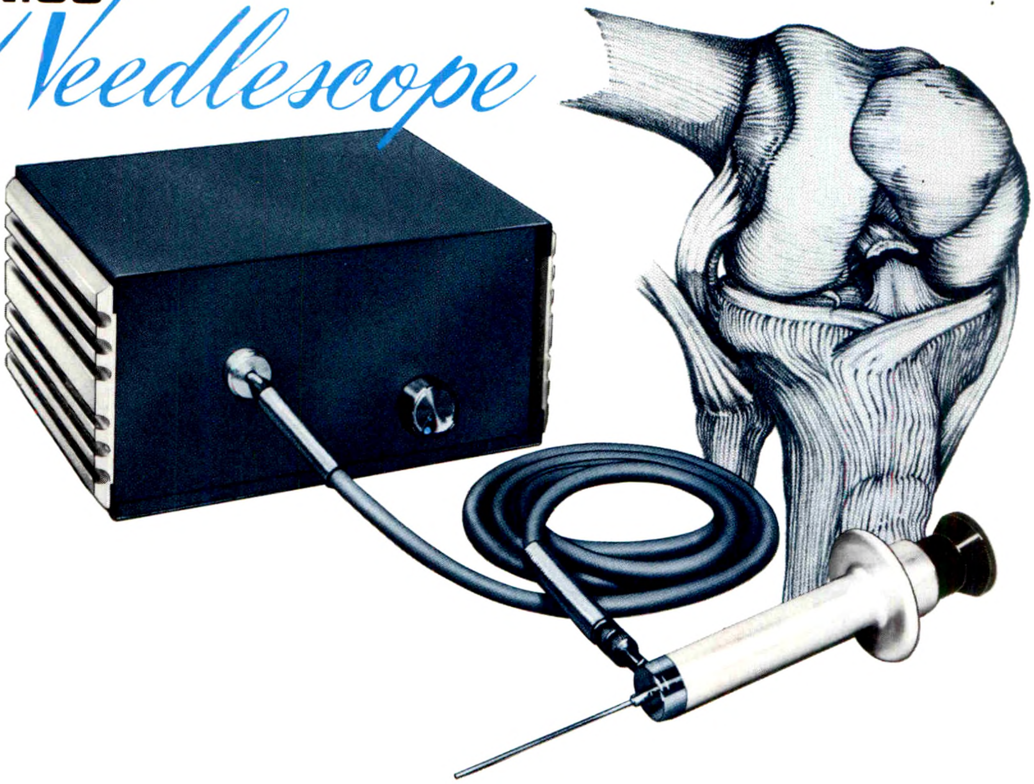
General: Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

HOW SUPPLIED: Ketalar solutions containing the hydrochloride in concentrations equivalent to ketamine base are available in 5, 10, 20, and 50 ml. vials. These vials contain 100, 50, 10, and 10 mg./ml., respectively. Each vial is supplied individually and in cartons of 10.

LG

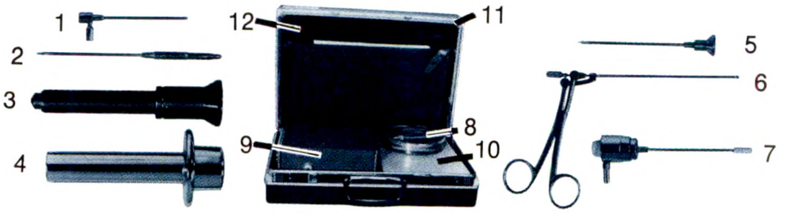
PARKE-DAVIS
PARKE, DAVIS & COMPANY Detroit, Michigan 48232

DYONICS *Needlescope*



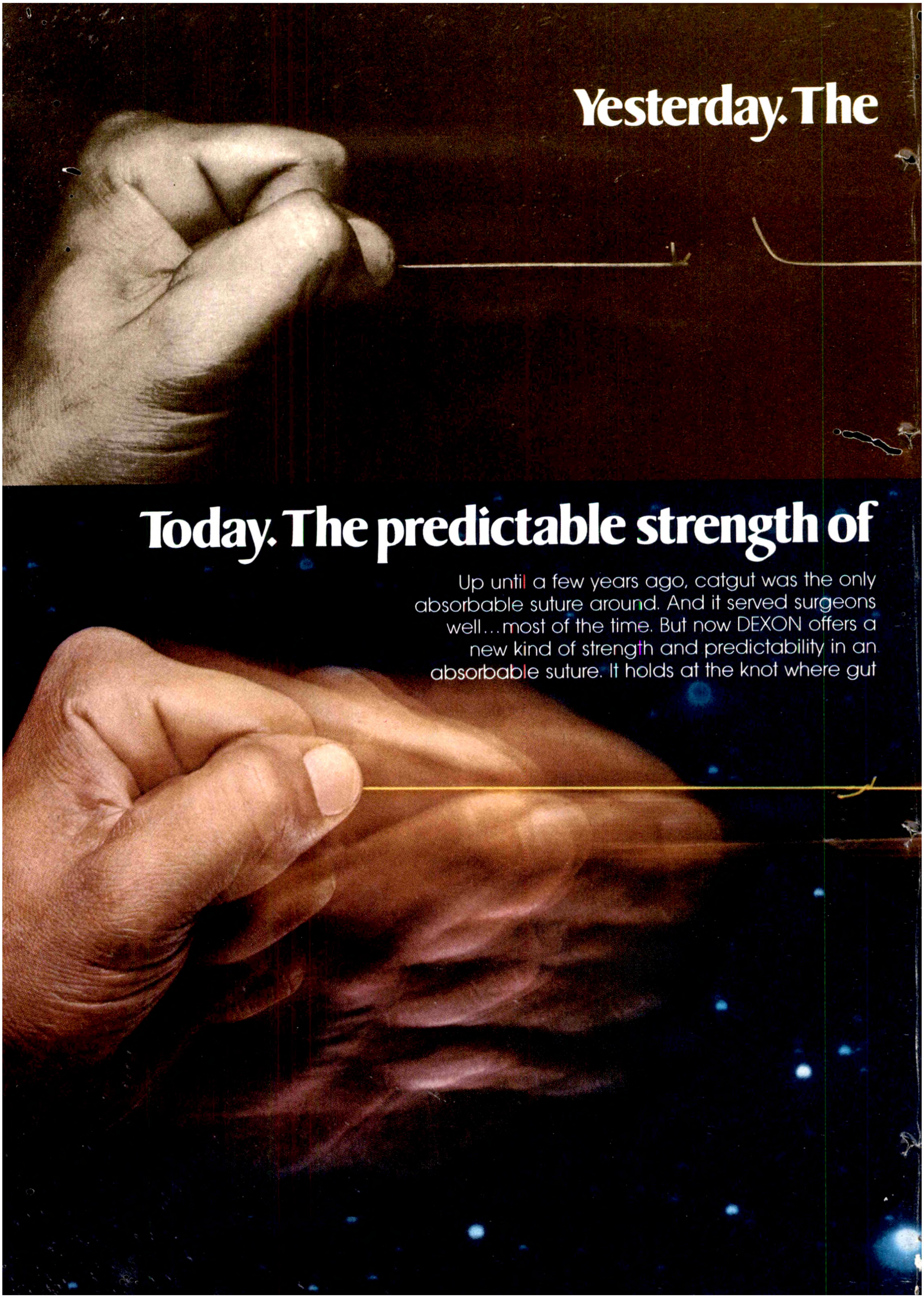
Direct visualization of the joints via arthroscopy has been shown to aid the surgeon in the identification and localization of pathology. This diagnostic technique previously required general anesthesia and involved considerable trauma resulting from the incision necessary to admit the conventional, large diameter (10mm) viewing needle.

The Dyonics Needlescope utilizes an extraordinarily thin (1.7mm) optical inserting needle made possible by the development of a patented, self-focusing rod lens. The special properties of this lens allow visualization of a target very close to the tip as well as at a distance with a depth of focus 1.0mm to near infinity and a field of view of 55 degrees. No incision is required and the diagnostic procedure may be performed under local anesthesia. The Needlescope ensemble shown below provides all the necessary components requisite to joint arthroscopy, including a high intensity light source and fiber optic light guide for optimum illumination of the joint cavity.



1. Cannula
2. Obturator
3. Ocular Assembly
4. Handle
5. Trocar
6. Biopsy Forceps
7. Optical Needle
8. Light Guide
9. Light Source
10. Instrument Case
11. Carrying Case
12. Instruction Manual

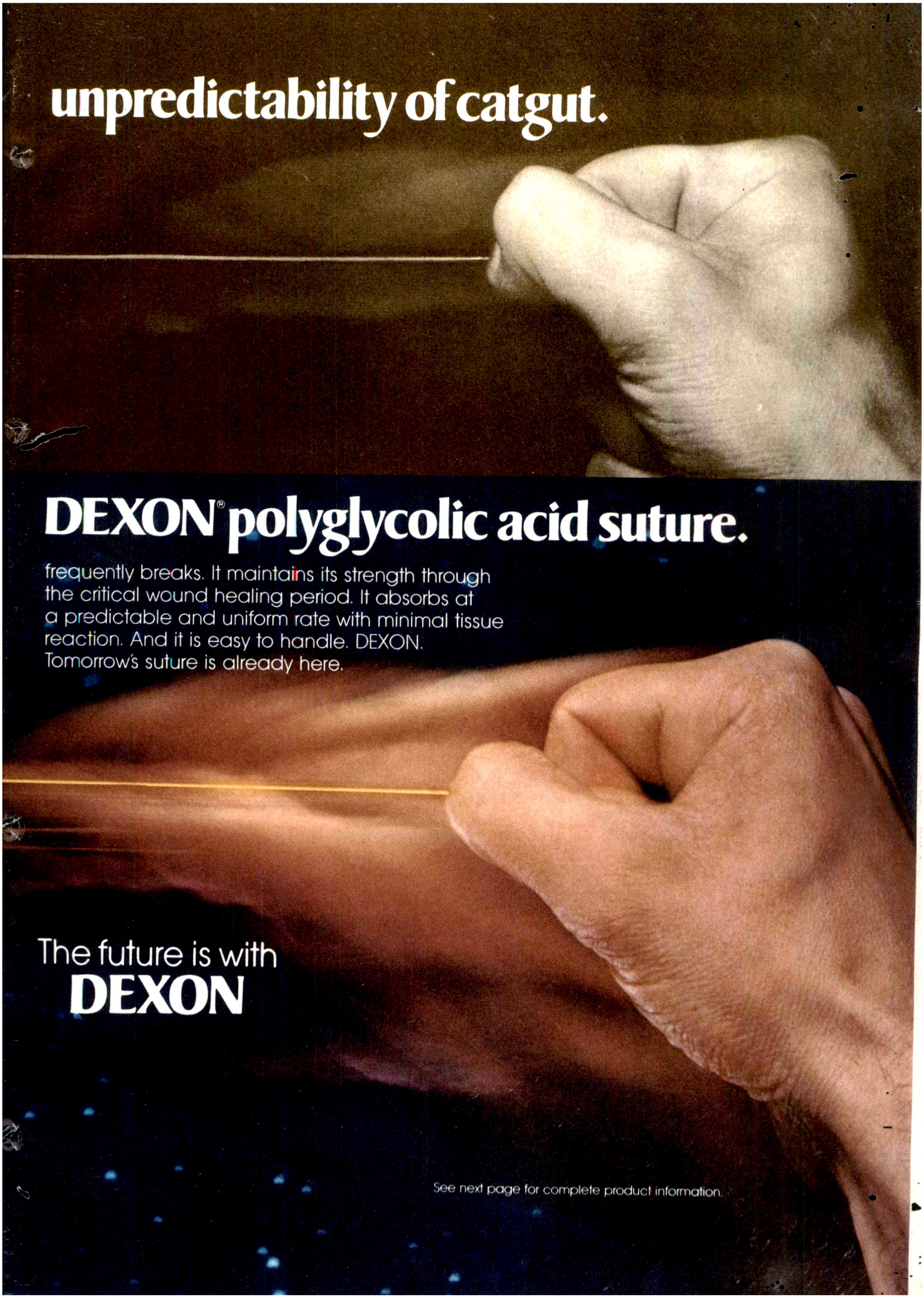
RICHARDS MANUFACTURING COMPANY, INC.
1450 BROOKS RD., MEMPHIS, TENN. 38116, A.C. 901 • 396-2121
IN CANADA, RICHARDS SURGICAL LIMITED, 130 EAST DRIVE, BRAMALEA, ONTARIO, L6T 1C3, (416) 677-9744
© RICHARDS MANUFACTURING CO., INC. 1973
PRINTED IN U.S.A.



Yesterday. The

Today. The predictable strength of

Up until a few years ago, catgut was the only absorbable suture around. And it served surgeons well…most of the time. But now DEXON offers a new kind of strength and predictability in an absorbable suture. It holds at the knot where gut



unpredictability of catgut.

DEXON® polyglycolic acid suture.

frequently breaks. It maintains its strength through the critical wound healing period. It absorbs at a predictable and uniform rate with minimal tissue reaction. And it is easy to handle. DEXON. Tomorrow's suture is already here.

The future is with
DEXON

See next page for complete product information.

Complete Product Information—Approved Official Package Insert

DESCRIPTION DEXON* polyglycolic acid Suture—Synthetic, Absorbable is a homopolymer of glycolic acid. The sutures are sterile, inert, noncollagenous, nonantigenic, nonpyrogenic, flexible, braided, undyed, with a natural beige color. They are uniform in size and tensile strength, but are smaller in diameter than Absorbable Surgical Sutures of equivalent tensile strength.

ACTIONS When DEXON is placed in tissues a minimal tissue reaction occurs, which is followed by a microscopic layer of fibrous connective tissue which grows into the suture material. Animal studies (subcutaneous tissue in rats, rabbits and dogs) revealed minimal absorption at 7 to 15 days, significant absorption at 30 days, and maximum resorption after 60 to 90 days. Tensile strength, not being a function of the absorption rate, may vary from tissue to tissue, depending in part on the rate of hydrolysis. The early tensile strength of DEXON is reported to be greater than that of comparable chromic catgut. In animal studies (subcutaneous tissue of rats, rabbits and dogs) there occurred a 30 to 50% loss of initial tensile strength in one week and 60 to 80% loss in two weeks, at which time as in the case with chromic catgut no useful residual tensile strength remains.

INDICATIONS DEXON sutures are indicated whenever absorbable sutures and ligatures are employed, provided that extended approximation of tissues is not required or where undue postoperative tension or stress is not anticipated. DEXON is also indicated where non-absorbable sutures are used for their characteristic lack of tissue reaction.

CONTRAINDICATIONS DEXON is contraindicated where extended approximation of tissues under strain must be maintained.

WARNINGS The safe use of this suture in cardiovascular, neural and ophthalmological surgery has not been established. Under certain circumstances, notably orthopedic procedures, immobilization by external support may be employed at the discretion of the surgeon. Do not resterilize. Discard opened, unused sutures.

PRECAUTIONS Acceptable surgical practice should be followed with respect to drainage and closure of infected wounds. DEXON suture knots must be properly placed to be secure. Therefore, place first throw in precise position for final knot, using a double loop, tie second throw square using horizontal tension; additional throws may be used as desired. Skin sutures which remain in place for periods of longer than seven days may cause localized topical irritation and the extended portion of suture may be snipped off after five to seven days, as indicated.

ADVERSE REACTIONS Those reactions that have been reported include tissue reaction or inflammation, fibrous or granulation tissue, wound separation and bleeding and accumulation of fluid around subcuticular stitches.

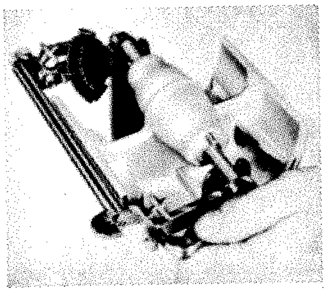
DOSAGE AND ADMINISTRATION Use as required. Do not resterilize. Discard opened, unused sutures.

HOW SUPPLIED Suture sizes 6-0 through 1. Supplied in cut lengths or ligating reels, non-needled or affixed to the various Davis & Geck ATRAUMATIC* needles in three dozen packages.

Rev. 6/73

DG
DAVIS+GECK
American Cyanamid Company
Pearl River, N.Y. 10965

PADGETT MANUAL
DERMATOME



ALUMINUM DRUM
Versatile
Guaranteed
Finest Quality

IMPROVED TO SIMPLIFY SKIN GRAFTING!

Accurate and uniform grafts up to 4 to 8 inches. Throw-away Blades, Dermatome Tape, and other accessories available for all models. Will take pattern grafts and will resplit grafts. Proven by thousands of Surgeons.

Write Today For Complete Information!

PADGETT DERMATOME DIVISION
2838 WARWICK TWFY., KANSAS CITY, MO. 64108

CHANGE OF ADDRESS

Change of Address: Please allow 60 days before date of issue for change of address. Notification should include the old as well as the new address, with indication of whether the change is temporary or permanent. Please give the name of the *Journal.*

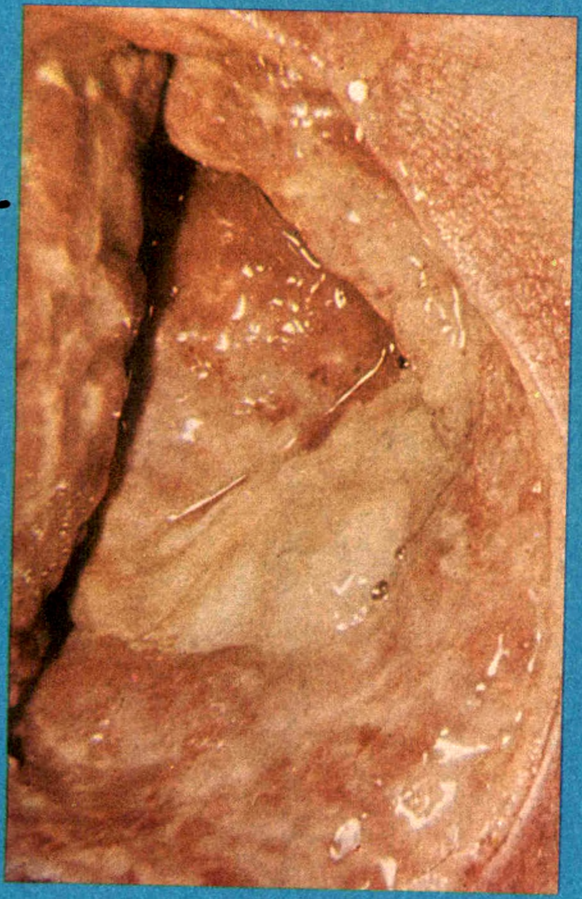
Send Change of Address cards to:

ANNALS OF SURGERY
c/o Fulfillment Manager
East Washington Square
Philadelphia, Penna. 19105

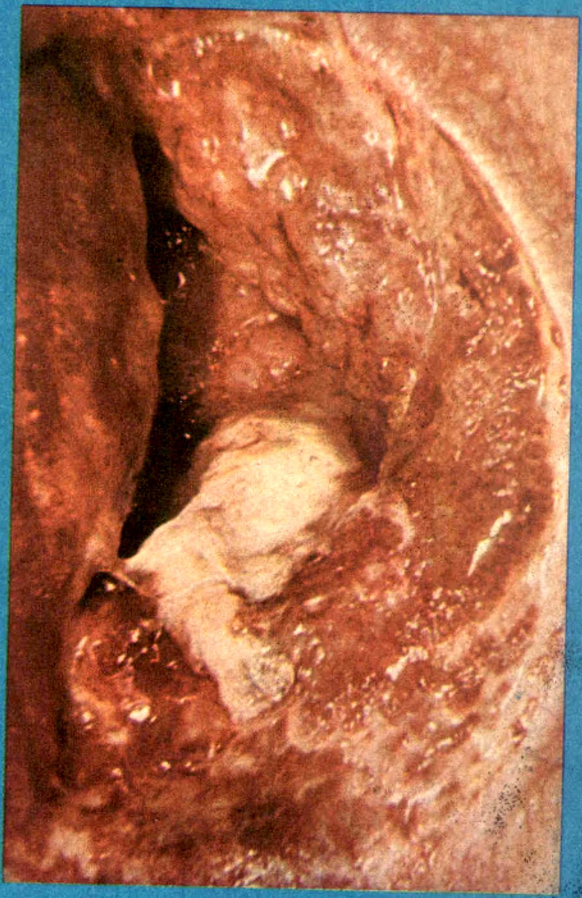
Decubitus Ulcers Yield to

Travase® Ointment

brand of **Sutilains**



Before treatment, necrotic matter coated the inner surfaces of this decubitus ulcer.



After six days of TRAVASE therapy, debridement is nearly complete and granulation evident.

Adjunctive Therapy—Observe Its Effects in 48 hours
When the recommended nursing technique is followed without deviation, this procedure can generate visible improvement within 48 hours of treatment. If no dissolution of slough occurs by then, further application is unlikely to be rewarding (recheck for break in procedure, usually due to use of cleansing or antiseptic agents which impair the effectiveness of the enzyme in TRAVASE).

Clinical observation and photos by Kathleen Brough Oldham, M.D., Marion County Home, Indianapolis, Ind.

Please see next page for prescribing information

First Class
Permit No. 39
Deerfield, Ill.

BUSINESS REPLY MAIL No Postage Stamp Necessary If Mailed in the United States

Postage Will Be Paid by Addressee

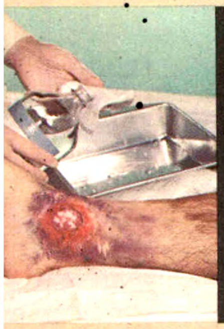
Flint Laboratories
Division of Travenol Laboratories, Inc.
200 Wilmot Road
Deerfield, Illinois 60015

ravase® Ointment brand of Sutilains

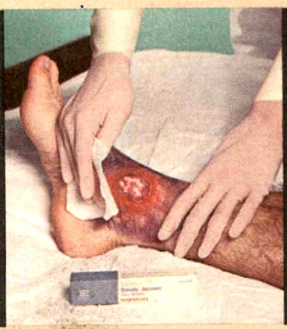
PPLICATION TECHNIQUE: TRAVASE Ointment is indicated as an adjunct o established methods of wound care for biochemical debridement. It issolves and facilitates the removal of necrotic tissues and purulent xudates.

RAVASE enzymes are selective. Virtually inactive on viable tissue.

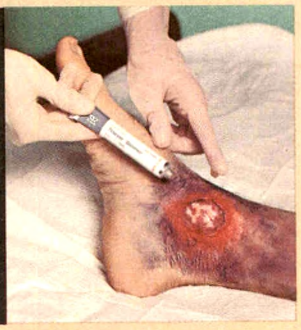
Vhen this recommended nursing technique is followed without deviation, his procedure can generate visible improvement within 48 hours . . .



cer being irrigated) oroughly cleanse and igate the wound area using ly sterile water or sodium oride solution. Be sure to anse the wound of any tiseptics or heavy-metal tibacterial agents which y interfere with the zyme activity.



Thoroughly soak the wound area. Where practical, tubbing or showering is suitable. Or wet soaks with gauze pads may be used. Remember to avoid chemical cleansing agents which may interfere with the therapy.



With a sterile cotton swab or finger cot, apply a very **thin** layer of TRAVASE Ointment. The ointment spreads easily and only a small amount is needed (a small dab of ointment will cover an area as big as the back of a hand).

Be sure, though, to rub the ointment well into every crack or crevice of the wound and overlap the surrounding skin one-fourth to one-half inch beyond the area to be debrided—to be sure of complete coverage.

pply loose, wet dressings, oroughly soaked in sodium hloride solution or sterile ater to the area to be ebrided only.

Cover the moist dressings with an occlusive wrap (Saran wrap, Telfa Pads, or other plastic wrappings) to keep wound site moist. Do not extend occlusive wrap over ½ inch beyond area to be debrided.

When changing dressing, gently wipe away the dissolved material. Repeat the complete dressing procedure, including application of TRAVASE Ointment, four times daily.

he ulcer shown in these photos is simulated on a model in order to demonstrate e correct TRAVASE application technique.

To: FLINT LABORATORIES
Division of Travenol Laboratories, Inc.
200 Wilmot Road
Deerfield, Illinois 60015

Name ____________________

Title ____________________

Institution ____________________

Street ____________________

City ____________________ State ____________ Zip ____________

Please send:

______ Additional Information on TRAVASE® Ointment (brand of Sutilains)

______ In-service training program

______ Comment ____________________

DESCRIPTION: TRAVASE® (brand of sutilains) Ointment is a sterile preparation of proteolytic enzymes, elaborated by **Bacillus subtilis,** in a hydrophobic ointment base consisting of 95% white petrolatum and 5% polyethylene. One gram of ointment contains approximately 82,000 casein units* of proteolytic activity.

ACTION: TRAVASE Ointment selectively digests necrotic soft tissues by proteolytic action. It dissolves and facilitates the removal of necrotic tissues and purulent exudates that otherwise impair formation of granulation tissue and delay wound healing (4).

At body temperatures these proteolytic enzymes have optimal activity in the pH range from 6.0 to 6.8.

INDICATIONS: For wound debridement (1,2)—TRAVASE Ointment is indicated as an adjunct to established methods of wound care for biochemical debridement of the following lesions:

Second and third degree burns,
Decubitus ulcers,
Incisional, traumatic, and pyogenic wounds,
Ulcers secondary to peripheral vascular disease.

CONTRAINDICATIONS: Application of TRAVASE (brand of sutilains) Ointment is contraindicated in the following conditions:

Wounds communicating with major body cavities,

Wounds containing exposed major nerves or nervous tissue,

Fungating neoplastic ulcers,

Wounds in women of child-bearing potential—because of lack of laboratory evidence of effects of TRAVASE upon the developing fetus.

WARNING: Do not permit TRAVASE Ointment to come into contact with the eyes. In treatment of burns or lesions about the head or neck, should the ointment inadvertently come into contact with the eyes, the eyes should be immediately rinsed with copious amounts of water, preferably sterile.

PRECAUTIONS: A moist environment is essential to optimal activity of the enzyme. Enzyme activity may also be impaired by certain agents. **In vitro,** several detergents and antiseptics (benzalkonium chloride, hexachlorophene, iodine, and nitrofurazone) may render the substrate indifferent to the action of the enzyme (3). Compounds such as thimerosal, containing metallic ions interfere directly with enzyme activity to a slight degree, whereas neomycin, sulfamylon-streptomycin, and penicillin do not affect enzyme activity. In cases where adjunctive topical therapy has been used and no dissolution of slough occurs after treatment with TRAVASE Ointment for 24 to 48 hours, further application, because of interference by the adjunctive agents, is unlikely to be rewarding.

In cases where there is existent or threatening invasive infection, appropriate systemic antibiotic therapy should be instituted concurrently.

Although there have been no reports of systemic allergic reaction in humans, studies have shown that there may be an antibody response in humans to absorbed enzyme material.

ADVERSE REACTIONS: Adverse reactions consist of mild, transient pain, paresthesias, bleeding and transient dermatitis. Pain usually can be controlled by administration of mild analgesics. Side effects severe enough to warrant discontinuation of therapy occasionally have occurred.

If bleeding or dermatitis occurs as a result of the application of TRAVASE (brand of sutilains) Ointment, therapy should be discontinued. No systemic toxicity has been observed as a result of the topical application of TRAVASE Ointment.

Dosage and Administration

STRICT ADHERENCE TO THE FOLLOWING IS REQUIRED FOR EFFECTIVE RESULTS OF TREATMENT

1. Thoroughly Cleanse and Irrigate Wound Area with sodium chloride or water solutions. Wound **MUST** be cleansed of antiseptics or heavy-metal antibacterials which may denature enzyme or alter substrate characteristics (e.g., Hexachlorophene, Silver Nitrate, Benzalkonium Chloride, Nitrofurazone, etc.).
2. Thoroughly moisten wound area either through tubbing, showering, or wet soaks (e.g., sodium chloride or water solutions).
3. Apply TRAVASE Ointment in a thin layer assuring intimate contact with necrotic tissue and complete wound coverage extending to ¼ to ½ inch beyond the area to be debrided.
4. Apply loose wet dressings.
5. Repeat entire procedure 3 to 4 times per day for best results.

How Supplied

3P3002 TRAVASE Ointment is supplied sterile in one-half ounce tubes (14.2 g.) containing 82,000 casein units of sutilains per gram of hydrophobic ointment base.

The ointment must be stored under refrigeration at 2° to 10° C (35° to 50° F).

References

1. Garrett, T. A. **Bacillus subtilis** protease, a new agent for debridement. Clin. Med. **76:** 11-15, 1969.

2. Hesterberg, R. (Necrosis treatment on fermentative basis). Doctoral dissertation from the Chirurgical Clinic of the University of Munich. Dissertation Printing: Charlotte Schoen, Munich, 1964. (Ger.)

3. Howes, E. L. The healing of the burn may be hindered by its first aid therapy. 20th Cong. Soc. Inter. Chir., Rome, Italy, September 14-23, 1963.

4. Prytz, B., Connell, J. F., Jr., and Rousselot, L. M. **Bacillus subtilis** protease in the digestion of burn eschar. Clin. Pharmacol. Therap. **7:** 347-51, 1966.

---

*A casein unit is the amount of enzyme required to produce the same optical density at 275 mμ as that of a solution of 1.5 mcg. tyrosine/m[illegible] after the enzyme has been incubated with 35 mg. of casein at 37° C. for one minute.

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Morton Grove, Illinois 60053

MONITORING
VERSATILITY TAILORED
TO YOUR NEEDS

Electrocardiograph
Start with the basic mobile ECG — solid-state; patient-isolated; automatic lead marking.

ECG with Monitor on Mobile Stand
Add the CS/515 Monitor/Heart Rate Meter and a stabilizer for the stand to give you a 1-bed ICU, or an ideal combination for surgery, recovery or emergency room.

Complete Compact Coronary Care Center
Add the defibrillator/synchronizer for a versatile low-cost combination for interim intensive care or graded stress-testing.

BURDICK'S MOBILE COMPACT CORONARY CARE CENTER
Burdick has developed a sensible and economical approach to building your monitoring capabilities tailored to need. It answers the three demands of sound operational economy — **mobility, versatility,** and **equipment utilization** between departments. Using the proven concepts of the Burdick CCCC you **buy** the components as you **need** them.

For a brochure and additional supportive data, contact your Burdick dealer or write **The Burdick Corporation, Milton, Wis. 53563.**

BURDICK®

"Current abstracts are amplified and illuminated by comments of the members of the Editorial Board, based on their own clinical experiences as well as those of other recognized authorities" . . . just one of the reasons why Lippincott's

REVIEW OF
SURGERY

helps Resident (special rate only $11.00) and Veteran Surgeon alike to keep up with current progress, trends, and attitudes in all branches of surgery and the surgical specialties.

A true saver of precious reading time—from its detailed Contents Pages to its meaty reviews, and abstracts especially classified for reader convenience—a typical issue includes:

- Focus—several Reviews of timely or other special significance
- An original Report of major importance
- Twenty or more Abstracts with Commentary (and oft-times, rebuttal)
- Residents Corner—comprising Brief (1 to 3-page) Reports and Investigations
- In-depth Reviews of Current Books in Surgery

TO PUT THE BIMONTHLY REVIEW OF SURGERY AT YOUR FINGERTIPS NOW,

SUBSCRIBE TODAY . . .

J. B. LIPPINCOTT COMPANY, P. O. BOX 1076, PHILADELPHIA, PA. 19105 A/S

Please enter my subscription to REVIEW OF SURGERY for 1 year (6 issues), at ☐ $15 (U.S. and Canada); ☐ $17 (all other countries); Resident Rate ☐ $11 (U.S. only; also note "year" of residency and Specialty ____________).

PLEASE PRINT

Name ____________

Address ____________

City/State/Zip ____________

☐ Payment Enclosed.

☐ Charge my account.

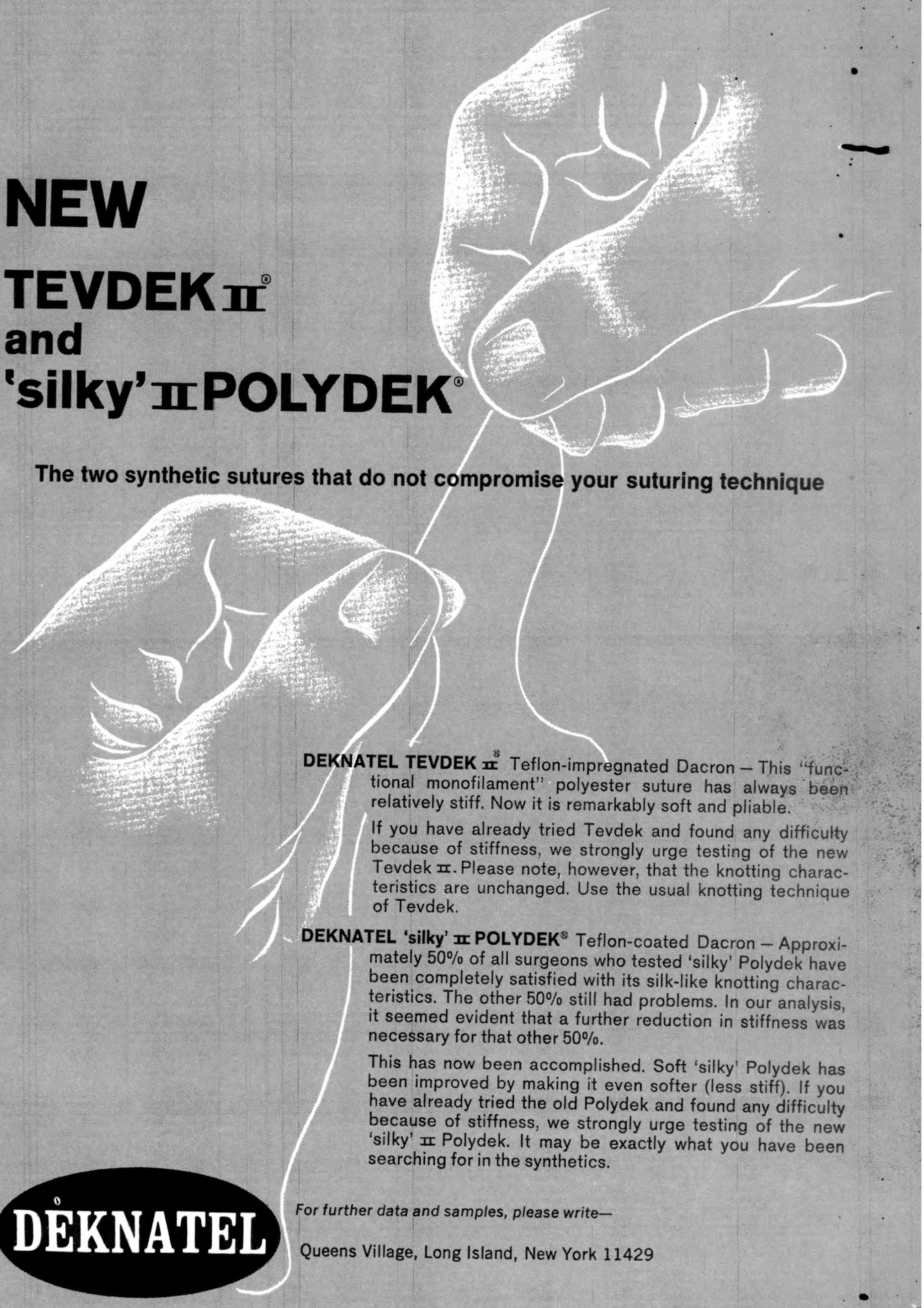
My Specialty is:

____

NEW

TEVDEK II®
and
'silky' II POLYDEK®

The two synthetic sutures that do not compromise your suturing technique



DEKNATEL TEVDEK II® Teflon-impregnated Dacron – This "functional monofilament" polyester suture has always been relatively stiff. Now it is remarkably soft and pliable.

If you have already tried Tevdek and found any difficulty because of stiffness, we strongly urge testing of the new Tevdek II. Please note, however, that the knotting characteristics are unchanged. Use the usual knotting technique of Tevdek.

DEKNATEL 'silky' II POLYDEK® Teflon-coated Dacron – Approximately 50% of all surgeons who tested 'silky' Polydek have been completely satisfied with its silk-like knotting characteristics. The other 50% still had problems. In our analysis, it seemed evident that a further reduction in stiffness was necessary for that other 50%.

This has now been accomplished. Soft 'silky' Polydek has been improved by making it even softer (less stiff). If you have already tried the old Polydek and found any difficulty because of stiffness, we strongly urge testing of the new 'silky' II Polydek. It may be exactly what you have been searching for in the synthetics.

DEKNATEL

For further data and samples, please write—

Queens Village, Long Island, New York 11429

INDEX TO ADVERTISERS

PHARMACEUTICAL SUPPLIES

- Abbott Laboratories
  - Surbex T 7A
- Boehringer Ingelheim, Ltd.
  - Dulcolax 46A,47A
- Bristol Laboratories
  - Blenoxane 41A,42A,43A,44A
- Burroughs Wellcome & Company
  - Empirin Cover IV
- Knoll Pharmaceuticals
  - Dilaudid 9A
  - Santyl 48A,49A
- Eli Lilly & Company
  - Darvon Comp. 21A
  - Keflex Cover III
  - Keflin 15A,16A
  - Loridine 50A,51A,52A
- McGaw Laboratories
  - Fre Amine 58A,59A
- Mead Johnson Laboratories
  - Mucomyst 12A,13A
- Parke-Davis Company
  - Ketalar 60A,61A,62A
- Purdue Frederick Company
  - Senokot 4A
- Reed & Carnick
  - Proctofoam 22A,23A
- Roche Laboratories
  - Berocca 45A
  - Valium 18A,19A,20A
- Schering Corporation
  - Garamycin 30A,31A,32A
- Winthrop Laboratories
  - Talwin 26A,27A,28A
- Wyeth Laboratories
  - Phenergan 2A,3A

SUPPLIES AND EQUIPMENT

- The Burdick Corporation 69A
- Davis & Geck
  - Dexon 64A,65A,66A
- Deknatel
  - Tevdek II & Polydek II 71A
- Eaton Laboratories
  - Vivonex 34A
- Ethicon, Inc.
  - Ligaclip 53A,54A,55A,56A
- Flint Laboratories
  - Travase 67A,68A
- Fuller Laboratories
  - Tucks 59A
- Golaski Laboratories, Inc.
  - Knitted Vascular Prosthesis 17A
- The Kendall Company
  - T.E.D. Stockings 35A,36A
- Meadox Medicals
  - Weavenit 33A
- Padgett
  - Manual Dermatome 66A
- Parke-Davis Company
  - Elase 24A,25A
  - Surgical Instruments Cover II
  - Support Hose 11A
- Purdue Frederick Company
  - Betadine Disposables 37A
  - Betadine Microbicides 1A
- Richards Mfg. Company
  - Needlescope 63A
- Sparta Instrument Corporation 40A
- Travenol Laboratories
  - Surgeons Gloves 14A
  - Viaflex 38A,39A

MISCELLANEOUS

- American College of Surgeons 57A
- S. Karger Ag 48A
- J. B. Lippincott Company 70A

Surgical Intervention for the Complications of Acute Myocardial Ischemia

E. D. MUNDTH, M.D., M. J. BUCKLEY, M.D., R. C. LEINBACH, M.D.,
H. K. GOLD, M.D., W. M. DAGGETT, M.D.,* W. G. AUSTEN, M.D.

From the Departments of Surgery and Medicine, Harvard Medical School and the General Surgical and Medical Services, Massachusetts General Hospital, Boston, Massachusetts

WITH CONVENTIONAL MEDICAL THERAPY the complications of acute myocardial ischemia, including myocardial infarction, impending myocardial infarction and recurrent ventricular tachyarrhythmia, are associated with a substantial morbidity and mortality.[2,11,31,33,34,36] Recent clinical experience with urgent surgical intervention, including mechanical circulatory assistance and myocardial revascularization, has been associated with a significant improvement in survival.[1,3,5,14,21,23,24,29,33,34] Although the indications for revascularization surgery in the treatment of chronic myocardial ischemia are reasonably well defined, selection criteria for operation, appropriate timing of surgical intervention and methods of surgical management are not as clearly defined for complications of acute myocardial ischemia. The present report summarizes our experience over the past 4 years with the surgical management of this group of patients.

Clinical Material

A total of 110 patients were included in this experience (Table 1). Patients were grouped into categories representing different complications of acute myocardial ischemia. In a few instances there was unavoidable overlap between groups because some patients had more than one complication of acute myocardial ischemia. To avoid duplication, we attempted to group patients according to their primary clinical problem. The clinical categories of acute myocardial ischemic complications were designated as follows: 1) myocardial infarction with cardiogenic shock, 2) evolving myocardial infarction, 3) impending myocardial infarction, 4) myocardial infarction with impending extension and 5) refractory ventricular tachyarrhythmias (Table 2).

One hundred of the 110 patients were initially admitted to the MIRU* Intensive Care Unit and underwent hemodynamic evaluation, diagnostic categorization and initial medical management. Twelve patients did not undergo initial hemodynamic evaluation in the MIRU unit but were similarly managed. Hemodynamic evaluation was achieved by monitoring the arterial blood pressure, pulmonary capillary wedge pressure, central venous pressure and serial dye dilution cardiac outputs. Arterial blood pressure was continuously monitored by a radial artery cannula and the pulmonary capillary wedge pressure was monitored by the Swan-Ganz flow directed catheter.[35] In addition, arterial blood gases, a 12-lead electrocardiogram, urine output, and serial serum CPK, SGOT and LDH enzyme levels were monitored.

Initial medical therapy for all complications of acute myocardial ischemia included 1) adjustment of the left-sided filling pressures to appropriate levels using the pulmonary capillary wedge pressure, 2) correction of arrhythmias by use of antiarrhythmic drugs and/or atrial or atrioventricular sequential pacing, 3) use of inotropic agents as epinephrine or levarterenol where necessary,

---

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25-27, 1973.

Reprint requests: Dr. Mundth, Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts 02114.

Supported in part by USPHS HL-12489-03, MIRU Contract #43-67-1443 and Program Project USPHS HE-06664.

* Established Investigator, American Heart Association.

* Myocardial Infarct Research Unit.

TABLE 1. *Clinical Aspects of 110 Patients Undergoing Surgery for the Complications of Acute Myocardial Ischemia*

Total No. Patients	110
Average Age	51
(Range)	39–60
Males:Females	4:1
History of Symptomatic Coronary Artery Disease	92 (85%)
Percentage of Coronary Admissions to Coronary Care Unit During Same Period of Time (4 Years)	110/1280 (8%)

TABLE 2. *Complications of Acute Myocardial Ischemia—110 Patients*

1. Myocardial Infarction with Cardiogenic Shock (80)
2. Evolving Myocardial Infarction (8)
3. Impending Myocardial Infarction (12)
4. Myocardial Infarction with Impending Extension (9)*
5. Refractory Ventricular Tachyarrhythmias (7)**

* Included are two patients with cardiogenic shock.
** Included are four patients with cardiogenic shock.

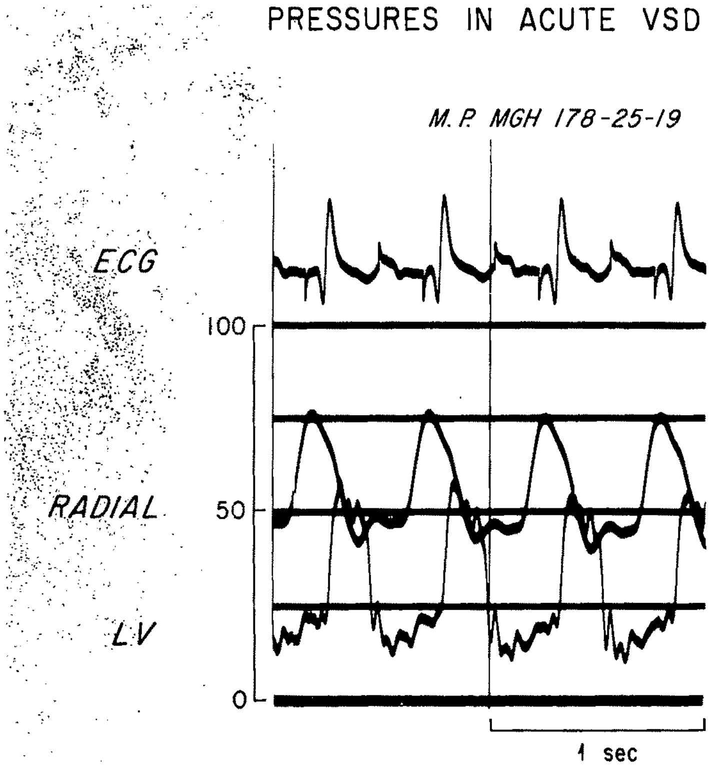


FIG. 1. Monitor tracings taken during coronary angiographic study in a patient with acute myocardial infarction, ruptured ventricular septum and severe cardiogenic shock. Note the peak left ventricular systolic pressure of 50 mm. Hg with diastolic augmentation of the radial artery pressure to 75 mm. Hg. by continuous IABP during the study, demonstrating the essential supportive rôle of IABP in cardiogenic shock. *Reproduced by permission from:* Gold, H. K., Leinbach, R. C., Sanders, C. A., *et al.*: Intra-aortic Balloon Pumping for Ventricular Septal Defect or Mitral Regurgitation Complicating Acute Myocardial Infarction. Fig. 6, *Circulation,* 47:1191, 1973.

4) correction of respiratory insufficiency by ventilatory support, 5) diuresis or digitalization where needed, 6) use of nitrates and β-adrenergic blockade with propranolol for ischemic recurrence and 7) bed rest, oxygen and sedation as indicated.

In order to achieve hemodynamic support and allow safe diagnostic angiographic study, mechanical circulatory assistance using the intra-aortic balloon pump[*] was instituted in 98 of the 110 patients. Some degree of diastolic blood pressure augmentation and systolic unloading was achieved in each instance. Complete diagnostic angiographic study including selective cine coronary angiography and left ventricular angiography was performed in each instance. The protective support of continuous IABP was utilized during 98 of the 110 studies and greatly facilitated safe, complete diagnostic study (Fig. 1).[16] Following a brief period of stabilization, further surgical intervention was undertaken in 67 (61%) of the 110 patients. Results of operation, establishment of criteria for patient selection, timing of operation and determination of effective surgical procedures are discussed separately within the five different diagnostic categories.

1. *Myocardial Infarction with Cardiogenic Shock*

Eighty patients with cardiogenic shock complicating acute myocardial infarction comprised this group.[17] One or more of the following clinical manifestations was present in all patients:

1) Arterial hypotension with systolic BP $<$ 90 mm. Hg.
2) Urinary output $<$ 20 cc./hr.
3) Decreased peripheral perfusion manifested by peripheral vasoconstriction and varying degrees of mental obtundation.

An attempt was made to define the severity of shock by objective hemodynamic measurement. The stage of shock was defined by taking into consideration the left ventricular stroke index and pulmonary capillary wedge pressure (Fig. 2).[10,17]

Because of persistent cardiogenic shock despite medical therapy, IABP was instituted in all of the 80 patients. Hemodynamic measurements before IABP were compared to the peak effect of IABP in 40 patients. IABP accomplished a mean increase in cardiac index of 0.8 L/min/M^2 (44%), a mean decrease in the pulmonary capillary wedge pressure of 5 mm. Hg (23%) and an average increase in mean aortic pressure of 7 mm. Mg (10%)[10] (Table 3). With periods of IABP varying from 2 to 10 days, 12 patients initially in cardiogenic shock became hemodynamically IABP-independent allowing successful weaning of the balloon. Ten of these 12 patients survived. Ten of the 12 patients were in Stage III shock and two were in Stage IV shock. Sixty-eight (85%) of the original 80 patients remained IABP-dependent and could not be weaned from IABP. IABP-dependence was defined as 1) mean aortic pressure < 60 mm. Hg 2) cardiac index < 2 L/min/M^2 and the pulmonary capillary wedge > 20 mm. Hg with IABP temporarily dis continued. The peak hemodynamic effect of IABP appears to occur within 24 to 48 hours after institution of IABP. Hemodynamic deterioration despite continued IABP occurred beyond that time in several instances. Angiography was undertaken urgently with the adjunct of continuing IABP in 52 patients. Thirty-five patients were judged operable and 17 patients inoperable. Operability was primarily based upon the presence of a bypassable vessel with adequate run-off in the region of the ischemic myocardium.[17] The left anterior descending coronary artery (LAD) was significantly involved in all patients and the dominant right coronary artery (RCA) in 21. Significant circumflex disease was present in five patients but in each instance the circumflex was nondominant and the distal vessels were small. The left ventricular angiograms uniformly showed a moderate to severely dilated left ventricle with severe regional hypokinesis and/or akinesis. The decision to proceed with revascularization and/or resection was not uniformly made at any given point during the patient's course. It readily became apparent that appropriate candidates for operation had an improved salvage when operated upon earlier in their clinical course. Of the 16 patients not undergoing angiographic study, all died of cardiogenic shock despite continued IABP. In each case, IABP-dependence persisted and the response to circulatory assistance gradually diminished. In our later experience, the decision regarding IABP-dependency was made within 24 hours, when possible. With hemodynamic IABP dependence, operation was recommended if the angiographic anatomy was demed operable. Where operation was refused, IABP-dependent patients uniformly died despite continued IABP. A total of 35 patients, including 27 patients undergoing preoperative hemodynamic study in the MIRU unit, accepted surgical treatment. Thirty-three underwent revascularization with one, two or three saphenous vein coronary bypass grafts, two patients had infarctectomy only and revascularization was combined with infarctectomy in 17 patients (49%). The decision regarding infarctectomy was made at the time of operation. Three factors which have been accepted as indications for infarctectomy are 1) the presence of a paradoxically bulging acute aneurysm which appears to interfere with left ventricular dynamics, 2) presence of a thinned out necrotic infarct in which rupture apears imminent and 3) localized infarct associated with recurrent ventricular arrhythmias.[8,21] Rupture of the interventricular septum was present in five patients and the ventricular septal defect was closed in association with infarctectomy and ventriculotomy closure.[5] A patch was not used in any instance. Two of these patients survived. Mitral valve replacement was necessary in addition to revascularization in two patients because of papillary muscle rupture or dysfunction and severe mitral regurgitation. Two of these patients survived. All but four patients in this group were in Stage IV cardiogenic shock prior to operation. Acute survival and discharge was accomplished in 13 patients (37%) and late survival with follow-up study ranging from 1 year to 3 years was accomplished in 10 patients (29%). Two of the late deaths were due to coronary artery disease and left ventricular failure, although one death was due to an unrelated cause. Of the 52 angiographically studied shock patients, 17 were judged inoperable and all died despite continued IABP.

---

[*] MGH-AVCO Intra-Aortic Balloon Pump.

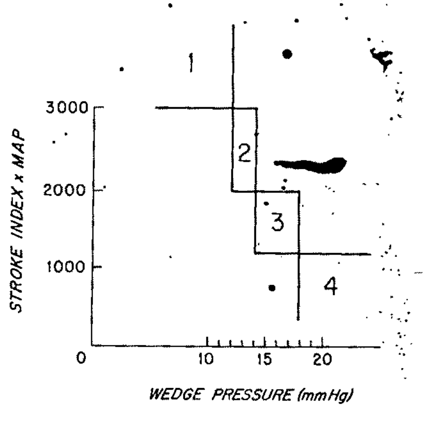


FIG. 2. Hemodynamic staging of cardiogenic shock. *Reproduced by permission from:* Leinbach, R. C., Gold, H. K., Dinsmore, R. E., *et al.:* The Role of Angiography in Cardiogenic Shock. Fig. 1, *Circulation* (In press).

TABLE 3. *Hemodynamic Changes with IABP in Cardiogenic Shock—(40 Patients)*

	IABP* Off	Peak* Effect IABP	Per cent Change
Cardiac Index (L/Min/M^2)	1.8	2.6	↑44%
Mean Aortic Pressure (mm. Hg)	67	74	↑10%
Pulmonary Capillary Wedge Pressure (mm. Hg)	22	17	↓23%

* Mean Values.

The mortality, even subsequent to successful weaning from IABP, was considerable over the course of 1 year follow-up study.[10,29] Ten patients became IABP-dependent and were successfully weaned with recovery from cardiogenic shock. However, three of the ten patients subsequently had further myocardial infarctions and died less than 1 year after initial infarction and shock. This has prompted consideration of elective revascularization, at an interval, in all patients who recovered from myocardial infarction shock with IABP alone. At the present time, only one patient has been

TABLE 4. *Selection Criteria for Revascularization in Treatment of Acute Myocardial Infarction and Cardiogenic Shock*

I. Clinical Criteria
  1. Beneficial response to IABP with objective hemodynamic improvement—indicative of potential myocardial functional reserve.
  2. Hemodynamic dependence on IABP persisting 24 to 48 hours—plateau of hemodynamic status with cardiac index < 2 L/Min/M², PC wedge > 20 mm. Hg or mean aortic pressure < 60 mm. Hg with IABP temporarily discontinued.
  3. Relatively short duration of shock (<12–24 hours).
  4. Relatively short time interval from onset of MI or extension of MI (<5 days).

TABLE 5. *Selection Criteria for Revascularization in Treatment of Acute Myocardial Infarction and Cardiogenic Shock*

II. Angiographic Criteria
  1. Some vascularity of hypo- or akinetic area of LV wall with reconstructible major coronary branch supplying area.
  2. Reconstructible proximal focal coronary artery disease.

TABLE 6. *Location of Evolving Myocardial Infarction, Angiographic Findings, and Surgical Results in 8 Patients*

Location MI	Complication	Angiographic Significant Disease LAD	RCA	CF	Bypass Grafts	Results
Ant.	V.F., Refractory	+			LAD	S
Ant.	V.F., Shock	+	+		LAD, RCA	D
Ant.	V.F., Shock	+	+	+	LAD, RCA, CF	D
Ant.	V.I.	+	+		LAD, RCA	S
Post. Lat.	Hypotension	+	+	+	LAD, RCA, CF	S
Inf.	Hypotension	+	+	+	LAD, RCA, CF	S
Inf.	Hypotension	+	+		LAD, RCA	S
Inf.	Cont'd. Pain	+	+		LAD, RCA	S

Ant. = Anterior, Post. Lat. = Posterolateral, Inf. = Inferior, V.F. = Ventricular Fibrillation, V.I. = Ventricular Irritability, LAD = Left Anterior Descending Coronary Artery, RCA = Right Coronary Artery, CF = Circumflex Coronary Artery, S = Surviving, D = Dead.

managed in this way, and has had an excellent result 8 months after revascularization operation.

The functional results of surgical treatment in those patients who survived generally have been excellent. Of the 10 long-term survivors (8 months to 3 years), eight have had excellent functional results, being able to work without angina or cardiac failure. One of the remaining two patients has mild recurrent angina but is able to work and one patient has mild symptoms of cardiac failure. Although experience to date indicates that a significant number of patients with acute myocardial infarction and cardiogenic shock can be salvaged by the combined therapeutic approach of temporary intra-aortic balloon pump assistance and urgent myocardial revascularization, selection of patients for operation and determining the proper timing of these therapeutic interventions remains difficult. Continuing clinical experience has provided certain guidelines for patient selection based upon clinical, hemodynamic (Table 4) and angiographic criteria[13,17,21,29] (Table 5). The relative time interval that is optimal in terms of making these decisions is not yet well defined. Clinical experience, as well as laboratory study,[19] has suggested that expediency is important. The earliest possible time when revascularization can be performed should provide the greatest benefit to the ischemic myocardium and prevent extension of infarction and subsequent progressive left ventricular functional impairment.

2. *Evolving Myocardial Infarction*

Eight patients with evolving myocardial infarction precipitated at the time of coronary angiography were operated upon urgently and underwent coronary artery revascularization. All eight patients were believed to have coronary artery disease and because of increasing angina were being evaluated for consideration of elective revascularization surgery. Although symptoms of angina in four of the patients increased in frequency, none were so unstable as to be classified as having impending infarction prior to catheterization. The electrocardiograms in each patient showed no evidence of acute or evolving changes prior to angiographic study. In four patients, dissection of a major coronary artery occurred which involved the main left coronary artery (LCA) in one patient, the left anterior descending coronary artery (LAD) in two and the right coronary artery (RCA) in one. A particulate embolus to a major coronary artery (both LAD) and suspected spasm or temporary catheter occlusion of the RCA was thought to be the mechanism which produced ischemia in the remaining four patients. All patients complained of angina and did not obtain immediate relief from nitroglycerine or morphine. Electrocardiographic changes of ischemia appeared in association with pain and evolved into an early infarct pattern in the distribution of the involved vessels. All eight patients developed ventricular irritability and three developed refractory ventricular fibrillation requiring external cardiac massage. These three patients were rushed to the operating room with continuing external cardiac massage, placed on cardiopulmonary bypass and coronary artery bypass grafts were constructed to significantly diseased vessels. One of these three patients survived (LCA dissection with LAD bypass) and is well 2 years after operation. It is noteworthy that the remainder of this patient's coronary artery system was grossly normal. The two patients that died could not be discontinued from cardiopulmonary bypass. The remaining five patients were operated upon from within 3 hours to 48 hours after the complication occurred. All five patients demonstrated some complications of the ischemic injury. Three patients became marginal hemodynamically with moderate hypotension, vasoconstriction and decreasing urine output; one patient continued to have episodes of ventricular tachycardia and the other had continuing pain. All underwent 1, 2 or 3 bypass grafts based upon the extent of each individual's coronary disease (Table 6). All hemodynamically significantly involved major coronary arteries (luminal narrowing > 75% normal diameter) were bypassed as well as the involved vessel. All five patients survived and have had excellent results without angina or cardiac failure. In two of the five patients, a small transmural infarction continued to evolve based on electrocardiographic changes in the early postoperative period.

Based upon this experience and that of others,[30,32,33] we would recommend urgent coronary arterial revascularization in this group in which the coronary anatomy is defined and there is an opportunity to avert the progression to major myocardial infarction. In particular, urgent revascularization surgery is indicated in those patients who have developed hemodynamic difficulties, refractory ventricular irritability or clinical evidence of an extending infarction.

3. *Impending Myocardial Infarction*

Certainly, much of the controversy related to indications for urgent revascularization surgery in this group is related to the difficulty of defining the syndrome of impending infarction. In puristic terms, the diagnosis can be made only in retrospect. However, clinical studies have well documented an intermediate syndrome of acute coronary insufficiency which, if prolonged, progresses to frank myocardial infarction.[2,34,36] Twelve patients, over the past 2 years, were classified by the clinical criteria recently accepted by a cooperative MIRU study as having impending myocardial infarction and were treated surgically. The criteria used for definition of impending myocardial infarction were 1) pain which lasted longer than 30 minutes, 2) electrocardiographic ST and T wave changes of ischemia associated with one or more pain episodes and 3) no evidence of evolution of infarction by serial electrocardiograms or enzymes. There were 10 men and two women. All 12 patients had had previous angina and in most, there was a recent history of an increase in frequency and severity of angina prior to the episode. There was a history of a previous myocardial infarction in seven and the majority were admitted to the coronary care unit to rule out evolving myocardial infarction. Recurrent episodes of severe coronary insufficiency occurred in each patient during hospitalization despite medical management including bed rest, oxygen, nitroglycerine, isosorbide dinitrate, propranolol and sedation. Hemodynamic studies in these patients before and during an episode of pain clearly demonstrated an acute rise in mean aortic pressure and of the pulmonary capillary wedge pressure (PCWP) during pain, associated with a slight reduction in cardiac index.[12] During the episodes of pain the PCWP frequently increased to > 25 mm. Hg with dyspnea, sweating, vasoconstriction and ventricular irritability. Because of the marginal hemodynamic status of these patients and the risk of coronary angiography with ongoing myocardial ischemia, IABP was introduced in 11 of the 12 patients. IABP effectively abolished pain, reversed electrocardiographic ST and T wave changes of ischemia and improved the altered hemodynamics in nine of the 11 patients undergoing IABP preoperatively (Fig. 3). In two patients, IABP significantly reduced pain and the electrocardiographic changes of ischemia but did not abolish them. Pain and/or electrocardiographic changes of ischemia reappeared with temporary discontinuation of IABP in six patients. In one patient, pain and ECG changes of ischemia persisted despite IABP, nitroglycerine and propranolol and revascularization was undertaken urgently. Complete angiographic study was carried out safely in all patients and surgical revascularization was advised. In one patient, IABP was not instituted prior to study because of failure to recognize impending myocardial infarction. Anesthesia was complicated by hypotension and ventricular arrhythmias, requiring institution of early cardiopulmonary bypass. IABP was required to hemodynamically stabilize the patient coming off cardiopulmonary bypass. Revascularization was carried out without complication in the remaining 11 patients, with 12 survivors. Operation was performed within 24 to 96 hours from the episode of prolonged pain but was not considered an emergency. The LAD was involved with significant disease in all patients and the RCA in nine. One, two or three bypass grafts were constructed to significantly diseased major coronary arteries in each instance. In this group of patients, postoperative electrocardiograms indicated no progression of ischemic changes to infarction and at the time of discharge, there were only nonspecific ST and T wave changes present in some patients.

At follow-up study ranging from 2 months to 1½ years, nine patients are completely free of angina. Angina recurred in three patients, to a mild degree in two and moderately severe in one. The latter patient underwent angiographic restudy which demonstrated an occluded LAD graft and a patent RCA graft. Reoperation was performed with construction of a new LAD graft. This patient remains free of angina 4 months following the second procedure.

The use of IABP has clearly facilitated management of this critically brittle group of patients in terms of safe angiographic study and safe induction of anesthesia.[12]

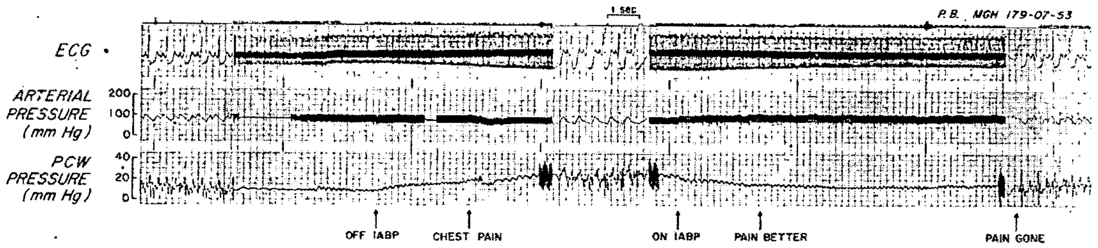


FIG. 3. Reversal of acute myocardial ischemia in a patient with impending myocardial infarction. Within 3 minutes of discontinuing IABP, the patient experienced pain with more marked depression of ST segments and a rise in PC wedge pressure to >20 mm. Hg. Resumption of IABP reversed the pain; the ischemic ECG changes and the PC wedge pressure returned to 12 mm. Hg.

Revascularization surgery in this group of patients with acute myocardial ischemia has proven to be effective and of no greater operative risk than elective revascularization surgery.[3,33,34]

4. *Myocardial Infarction with Impending Extension*

Recurrent pain of myocardial ischemia in the recovery phase of acute myocardial infarction may presage extension of the infarction with subsequent hemodynamic deterioration and increase in mortality. Nine patients with acute myocardial infarction developed recurrent ischemic pain associated with significant new ST segment changes of severe ischemia 5 to 7 days after onset of myocardial infarction. Similar to patients with impending infarction, medical therapy including short and long acting nitrates, β-blockade with propranolol, oxygen, sedation and morphine failed to control the ischemia. The established infarction was anterior in location in five patients, and inferior in four. In all of the patients studied, there was significant hemodynamic deterioration in association with ischemia. The pulmonary capillary wedge pressure (PCWP) rose significantly in each patient, and two patients developed progressive hypotension with eventual cardiogenic shock. In the latter two patients, the cardiac index was greatly reduced. Intra-aortic balloon pumping was started within 24 to 48 hours from the onset of recurrent ischemic pain. IABP abolished pain and improved hemodynamics in each patient. This included a rise in arterial blood pressure, a reduction in PCWP and increase in cardiac index. Pain and ST segment changes of ischemia reappeared within 10 minutes of stopping IABP in six patients and were again reversed by a further period on IABP. This suggested a strong dependency on IABP to reduce the left ventricular work load and to prevent myocardial ischemia.[12,24]

Coronary angiography was performed without complication in eight instances with the adjunct of continued IABP. In one patient, early in our experience, angiography was performed without IABP and the study was complicated by ventricular tachycardia, hypotension and new infarction. The arteriographic findings in this group indicated that occlusive disease was not only limited to the artery with distribution to the infarct but involved the other major coronary arteries as well, and jeopardized the collateral flow to the infarcted region or to the opposite left ventricular wall. The left anterior descending and right coronary arteries were significantly involved in all nine patients, the circumflex, in two patients and the main left coronary artery in one. Left ventricular angiography revealed extensive akinesis of the anterolateral wall and apex in the two patients who developed cardiogenic shock and marked hypokinesis of the anterior wall was present in two other patients with severe ventricular functional impairment.

In the first two patients in this series, cardiogenic shock ensued before IABP was started. The shock state was resolved by IABP, but both patients developed recurrent pain associated with hemodynamic deterioration on temporary interruption of circulatory assistance and urgent revascularization was carried out.

Saphenous vein bypass grafts were constructed to both the distal right coronary and left anterior descending coronary arteries in seven patients and a triple graft was done in the remaining two patients. In one of the latter patients who sustained a fresh infarction during catheterization, infarctectomy was combined with the triple graft but the patient could not be weaned from cardiopulmonary bypass. The other death in this series occurred as a result of unexplained postoperative acute renal failure. Seven patients survived and are free of angina from 2 months to 1½ years postoperatively.

5. *Refractory Ventricular Tachyarrhythmias*

Life-threatening ventricular tachyarrhythmias are relatively common after myocardial infarction and may recur despite medical therapy. Seven patients with medically refractory recurrent ventricular tachyarrhythmias after myocardial infarction were operated upon in the acute post-infarction phase, less than 6 weeks from the time of infarction. Medical therapy included the use of multiple antiarrhythmic agents, electrical countershock and overdrive pacing. The average interval from onset of myocardial infarction to onset of ventricular irritability was 12 days and medical management was continued an average of 20 days prior to operation. Four patients were hypotensive and intermittently in shock prior to operation. The pulmonary capillary wedge pressure was abnormally elevated in all seven patients and was over 20 mm. Hg in the four hypotensive patients. IABP was initiated preoperatively in the latter four patients with hemodynamic improvement. Although the frequency of ventricular tachyarrhythmias decreased with IABP, episodes of ventricular tachycardia continued to occur.[23] Coronary angiography revealed the left anterior descending coronary artery to be significantly involved in all seven patients, the right coronary artery in six patients and the circumflex, in two. Direct coronary arterial revascularization and/or resection of a left ventricular aneurysm or infarctectomy was performed in each patient. Six of the seven patients in the acute group underwent resection of the recent infarction and this procedure was combined with revascularization in two. In the remaining patient, revascularization only was performed. IABP was instituted at the time of operation or early postoperatively in the three patients that did not require assistance preoperatively. In all instances IABP was continued a minimum of 2 days postoperatively, with a range from 2 to 6 days. Significant hemodynamic assistance was gained in each instance evidenced by a reduction in mean left atrial pressure, augmentation of diastolic blood pressure with a corresponding decrease in peak systolic pressure and increase in cardiac output. IABP was weaned in the postoperative period when it was apparent the patient was hemodynamically stable and no longer IABP-dependent.

Four patients survived and three have had excellent clinical results without ventricular irritability, angina or cardiac failure on follow-up stuly ranging from 3 to 24 months. One of the four patients continues to have ventricular irritability and cardiac failure necessitating antiarrhythmic agents, digitalis and diuretics. Antiarrhythmic agents have not been required in the asymptomatic group.

Discussion

The clinical manifestations of acute myocardial ischemia depend upon the duration and severity of ischemia and the extent of myocardium involved. Brief episodes of acute myocardial ischemia are usually manifested as anginal attacks and although, when frequent, are symptomatically disabling are not associated with a serious threat to life. An increase in duration or severity of ischemia may lead to myocardial cellular death and infarction with a resulting increase in morbidity and mortality rates. Death from myocardial infarction is estimated to be 30 to 40% with about half of the deaths occurring before hospital admission.[11] The rate of hospital mortality of 15 to 20% is primarily related to complications of cardiogenic shock and ventricular arrhythmias.[11,31] Although continuous monitoring in coronary care units and careful medical management has reduced death from arrhythmias, it has had little effect on the rate of mortality from cardiogenic shock and progressive left ventricular failure. Clinical studies have shown that frequently there is an identifiable progression from severe ischemia to infarction, to extension, and eventually, left ventricular failure. The occurrence of a transmural myocardial infarction, with involvement of a substantial portion of the left ventricle, often causes a decrease in cardiac output and arterial hypotension. The reduction in coronary perfusion pressure further diminishes the anatomically restricted coronary blood flow and may, in time, add to the original ischemic injury by extension of the infarct initiating a vicious cycle of events. Page *et al.*[27] have demonstrated irregular and scattered areas of necrosis throughout the left ventricle, histologically of varying ages in patients dying of cardiogenic shock. This was interpreted as evidence of progressive extension of the initial infarction, which ultimately resulted in left ventricular power failure and death.

The use of inotropic agents in the treatment of acute myocardial ischemic complications may result in increased ischemia due to the increased myocardial oxygen demand, induced by the inotropic agent when oxygen delivery cannot be improved. Maroko *et al.*[20] have shown that the use of inotropic agents may actually increase the size of an experimentally produced infarct, although the initial effect was to increase myocardial contractility and augment arterial blood pressure. Beta-adrenergic blockade with propranolol has reduced the size of an experimentally produced infarct[20] but may be difficult to use clinically in patients with acute myocardial infarction because of subsequent decrease in myocardial contractility producing hypotension and worsening left ventricular failure.

Mechanical circulatory assistance, achieved by intra-aortic balloon pumping, effectively decreases myocardial oxygen requirements by reducing after-load, augmenting coronary blood flow in the ischemic heart.[15,28] As illustrated by the clinical experience in the present report and a previous report by Gold *et al.*,[12] acute myocardial ischemia can be reversed effectively by IABP. However, discontinuation of IABP resulted in a prompt recurrence of ischemia in the majority of patients. There has been no evidence from our experience that a period of circulatory assistance decreases the propensity for recurrent ischemia or increases the threshold of ischemia.

Although experimental studies have shown that IABP can reduce the size of an experimentally produced infarct if applied early,[18] there is as yet no clear evidence that IABP can reduce the size of infarction in the clinical setting. There is evidence, however, that the institution of IABP early in the course of an acute myocardial infarction may minimize infarct extension.[6] It also has been evident from our experience that IABP can interrupt the progression of acute myocardial ischemia allowing safe, complete angiographic study and provide a margin of safety during induction of anesthesia and operation.

The logic of coronary artery revascularization for acute myocardial ischemia without infarction is obvious. There has been legitimate reason, however, to question revascularization for actual infarction with the possibility of worsening ventricular function due to hemorrhage and edema in the infarcted area and the adjacent myocardium. Reperfusion studies in experimentally produced infarctions suggests that the size of the infarct can be reduced by coronary reperfusion within 6 hours of the time of coronary occlusion.[19,26] Clinically, when the actual time of occurrence of acute ischemic injury can be identified, it is possible to undertake revascularization during the first few hours of evolution of the myocardial infarct with the hope of reversing the gradual process of myocardial cellular death. When the ischemic injury occurs during angiographic study, early surgical intervention is facilitated by virtue of having the coronary angiogram available. Successful early revascularization was attained in six of eight patients in our experience with reversal of the evolving infarction in four. Scanlon *et al.*[30] and Smullens *et al.*[32] have reported similar results. Identification of an evolving myocardial infarction in the clinical setting, but not during catheterization study, is more difficult. In this situation, where indicated because of hemodynamic deterioration, emergency coronary angiographic study and revascularization should be carried out in as short a time span as possible. Cheanvechai *et al.*[3] reported experience with 24 patients operated upon within 4 to 10 hours after onset of acute infarction with only one death in a patient who developed cardiogenic shock preoperatively.

Some experimental evidence has suggested that revascularization of an infarct beyond 6 hours may be detrimental to left ventricular function.[4,9] However, pathologic study of the 22 hearts of patients who did not survive revascularization for cardiogenic shock in the present series revealed only three instances of hemorrhagic infarct. It was evident from the onset that acute revascularization in such patients was oriented toward improved perfusion of the adjacent ischemic peri-infarction zone of myocardium and was not intended to reverse an established infarct. As shown by Cox *et al.*[7] it is this zone of myocardium that may remain ischemic and progress to extension of the infarction. Although IABP temporarily may prevent extension of an infarction into the original peri-infarction myocardial zone, more definitive therapy to improve perfusion of this zone appears to be indicated in the majority of patients with acute myocardial infarction and cardiogenic shock.[17,22,25,29] From our earlier experience, survival with IABP alone for treatment of cardiogenic shock was little improved compared to conventional therapy.[10] The improved survival with IABP plus urgent revascularization has been encouraging and indicates the potential effectiveness of this method of approach. In analyzing our experience, the only consistent and significant factors related to success in this group of patients are shown in Tables 4 and 5.[4,17] The most important and significant factor was the presence of some vascularity in the hypokinetic or akinetic infarcted area with a reconstructable major coronary artery in this location.[17] Success can be attained in some instances even when the left ventricular angiogram reveals a markedly dilated poorly contracting ventricle.

It has become apparent from this experience with treatment of acute myocardial ischemic complications that *early* surgical intervention is of great importance. Intra-aortic balloon pump assistance is effective in temporarily reversing acute myocardial ischemia, is minimally invasive, causing little discomfort to the patient, and can be instituted rapidly within 1 hour of identification of an acute myocardial ischemic complication.[17] During the 4-year period of this study, the intra-aortic balloon could not be inserted, due to occlusive aortoiliac disease, in only four additional patients with complications of acute myocardial ischemia. IABP has proven to be hemodynamically effective and safe with only six identifiable complications; aortic dissection occurred in one patient and elevation of an atherosclerotic plaque in four patients, all of which were not identified clinically but found incidently at post-mortem examination; sepsis at the point of insertion and hemorrhage occurred in one patient requiring ligation of the femoral artery and arterial reconstruction. Thus, it is our policy to institute IABP as early as possible in the course of acute myocardial ischemic complication to allow clinical stabilization, safe diagnostic study and urgent operation if indicated. An exception to this in our view is the patient with evolving acute myocardial infarction with severe hemodynamic deterioration in whom the coronary anatomy is known from previous angiographic study. In this situation, the patient should undergo immediate operation.

This experience with the treatment of complications of acute myocardial ischemia also has demonstrated that IABP is primarily of temporary supportive value and more definitive surgical therapy is usually indicated in terms of revascularization surgery. It has become apparent that expediency is important here, also. Better clinical results can be expected with earlier definitive intervention in the complications of acute myocardial ischemia which in turn necessitates earlier clinical identification and prompt action.

Unquestionably, the results for surgical therapy of established myocardial infarction and cardiogenic shock are less optimal than for treatment of acute myocardial ischemia without extensive myocardial cellular death. Obviously there are some patients with massive established myocardial infarctions and cardiogenic shock that cannot be salvaged by any surgical means other than cardiac replacement. However, careful selection can identify a significant number of patients who may be salvaged by surgical treatment from a virtually hopeless prognosis with conventional therapy.

Summary

One hundred ten patients with complications of acute myocardial ischemia underwent surgical treatment including 80 patients with myocardial infarction and cardiogenic shock, eight patients with evolving myocardial infarction, 12 patients with impending myocardial infarction, nine patients with myocardial infarction and impending extension and seven patients with post-infarction refractory ventricular tachyarrhythmias.

IABP has been shown to temporarily reverse acute myocardial ischemia and has been an important adjunct in the management of these patients. IABP has been shown to be hemodynamically effective, minimally invasive and relatively safe.

Definitive revascularization surgery was performed in 35 patients in cardiogenic shock of whom 13 survived (37%). Six of eight patients with evolving acute myocardial infarction survived revascularization surgery and remain well. Twelve patients with impending myocardial infarction have undergone revascularization with no deaths and excellent late results. Seven of nine patients with acute myocardial infarction and impending extension survived operation and remain well. Four of seven patients with post-infarction refractory ventricular tachyarrhythmias survived operation and three of the four remain free of ventricular irritability, angina or cardiac failure.

Prompt identification of complications of acute myocardial ischemia and *early* surgical intervention is recommended for selected patients. Significant salvage and symptomatic improvement in this critical group of patients can be expected.

Acknowledgment

The authors wish to acknowledge the dedicated service of a large number of professional people involved in the care of this group of patients, without whom, the task would have been impossible. Special acknowledgment must be given to the MIRU staff, the coronary care and surgical intensive care unit staffs, the cardiac anesthesia staff, the cardiology staff, and the indefatigable cardiac surgical resident staff.

References

1. Abbas, S. Z., Shankar, K. R., Cohen, G., Akrekli, Y. and Keon, W. J.: Medical versus Surgical Management of Cardiogenic Shock. Am. J. Cardiol., 29:250, 1972.
2. Ambrust, C. A., Jr. and Levine, S. A.: Paroxysmal Ventricular Tachycardia: A Study of One Hundred and Seven Cases. Circulation, 1:28, 1950.
3. Auer, J. E., Johnson, W. O., Flemma, R. J., Tector, A. J. and Lepley, D., Jr.: Direct Coronary Artery Surgery for Impending Myocardial Infarction. Circulation, 44(Suppl. II):II-102, 1971.
4. Bresnahan, G. F., Shell, W. E., Ross, J., Jr., Roberts, R. and Sobel, B. E.: Deleterious Effects of Reperfusion in Evolving Myocardial Infarction. Circulation, 46:(Suppl. II): II-13, 1972.
5. Buckley, M. J., Mundth, E. D., Daggett, W .M., Gold, H. K., Leinbach, R. C. and Austen, W. G.: Surgical Management of Ventricular Septal Defects and Mitral Regurgitation Complicating Acute Myocardial Infarction. Ann. Thorac. Surg. In press.
6. Caulfield, J. B., Dunkman, W. B. and Leinbach, R. C.: Cardiogenic Shock. Myocardial Morphology with and without Artificial Left Ventricular Counterpulsation. Arch. Pathol., 93:532, 1972.
7. Cox, J. L., McLaughlin, V. W., Flowers, N. C. and Horan, L. G.: The Ischemic Zone Surrounding Acute Myocardial Infarction: Its Morphology as Detected by Dehydrogenase Staining. Am. Heart J., 76:650, 1968.
8. Daggett, W. M., Buckley, M. J., Mundth, E. D., Sanders, C. A. and Austen, W. G.: The Role of Infarctectomy in the Surgical Treatment of Myocardial Infarction. Am. Heart J., 84:723, 1972.
9. DeLoche, A., Fontaliran, F., Fabiani, J. N. and Carpentier, A.: Surgical Revascularization of Myocardial Infarction. J. Europ. Soc. Surg. Res. In press.
10. Dunkman, W. B., Leinbach, R. C., Buckley, M. J., Mundth, E. D., Kantrowitz, A. R., Austen, W. G. and Sanders, C. A.: Clinical and Hemodynamic Results of Intra-aortic Balloon Pumping and Surgery for Cardiogenic Shock. Circulation, 46:465, 1972.
11. Friedberg, C. K.: Diseases of the Heart. Edit. 3, Philadelphia, W. B. Saunders, Co., 1966, Chapt. 21, pp. 851–59.
12. Gold, H. K., Leinbach, R. C., Sanders, C. A., Buckley, M. J., Mundth, E. D. and Austen, W. G.: Intra-aortic Balloon Pumping for Control of Recurrent Myocardial Ischemia. Circulation, 47:1197, 1973.
13. Gold, H. K., Leinbach, R. C., Sanders, C. A., Buckley, M. J., Mundth, E. D. and Austen, W. G.: Intra-aortic Balloon Pumping for Ventricular Septal Defect or Mitral Regurgitation Complicating Acute Myocardial Infarction. Circulation, 47:1191, 1973.
14. Hill, J. D., Kerth, W. J., Kelly, J. J., Selzer, A., Armstrong, W., Popper, R. W., Langston, M. F. and Cohn, K. E.: Emergency Aortocoronary Bypass for Impending or Extending Myocardial Infarction. Circulation, 43(Suppl. I):I-105, 1971.
15. Leinbach, R. C., Buckley, M. J., Austen, W. G., Petschek, H. E., Kantrowitz, A. R. and Sanders, C. A.: Effects of Intra-aortic Balloon Pumping on Coronary Flow and Metabolism in Man. Circulation, 43(Suppl. I):I-77, 1971.
16. Leinbach, R. C., Dinsmore, R. E., Mundth, E. D., Buckley, M. J., Dunkman, W. B., Austen, W. G. and Sanders, C. A.: Selective Coronary and Left Ventricular Cine-angiography during Intra-aortic Balloon Pumping for Cardiogenic Shock. Circulation, 45:845, 1972.

17. Leinbach, R. C., Gold, H. K., Dinsmore, R. E., Mundth, E. D., Buckley, M. J., Austen, W. G. and Sanders, C. A.: The Role of Angiography in Cardiogenic Shock. Circulation. In press.
18. Maroko, P. R., Bernstein, E. F., Libby, P., DeLaria, G. A., Covell, S. W., Ross, J., Jr., and Braunwald, E.: Effects of Intra-aortic Balloon Counterpulsation on the Severity of Myocardial Ischemic Injury Following Acute Coronary Occlusion: Counterpulsation and Myocardial Injury. Circulation, 45:1150, 1972.
19. Maroko, P. R., Ginks, W. R., Libby, P., Sobel, B. E., Shell, W. E. and Ross, J., Jr.: Salvage of Myocardial Tissue by Coronary Artery Reperfusion Following Acute Coronary Occlusion. Am. J. Cardiol., 29:278, 1972.
20. Maroko, P. R., Kjekshus, J. K., Sobel, B. E., Watanabe, T., Covell, J. W., Ross, J., Jr. and Braunwald, E.: Factors Influencing Infarct Size Following Experimental Coronary Occlusion. Circulation, 46:465, 1971.
21. Mundth, E. D., Buckley, M. J., Daggett, W. M., Sanders, C. A. and Austen, W. G.: Surgery for Complications of Acute Myocardial Infarction. Circulation, 45:1279, 1972.
22. Mundth, E. D., Buckley, M. J., Leinbach, R. C., DeSanctis, R. W., Sanders, C. A., Kantrowitz, A. and Austen, W. G.: Myocardial Revascularization for the Treatment of Cardiogenic Shock Complicating Acute Myocardial Infarction. Surgery, 70:78, 1971.
23. Mundth, E. D., Buckley, M. J., DeSanctis, R. W., Daggett, W. M. and Austen, W. G.: Surgical Treatment of Ventricular Irritability. J. Thorac. Cardiovasc. Surg. In press.
24. Mundth, E. D., Buckley, M. J., Gold, H. K., Daggett, W. M., Leinbach, R. C. and Austen, W. G.: Intra-aortic Balloon Pumping and Emergency Coronary Arterial Revascularization for Acute Myocardial Infarction with Impending Extension. Ann. Thorac. Surg. In press.
25. Mundth, E. D., Yurchak, P. M., Buckley, M. J., Leinbach, R. C., Kantrowitz, A. and Austen, W. G.: Circulatory Assistance and Emergency Direct Coronary Artery Surgery for the Treatment of Cardiogenic Shock Complicating Acute Myocardial Infarction. N. Engl. J. Med., 283:1382, 1970.
26. O'Brien, C. M., Carroll, M., O'Rourke, P. T., Rhodes, E. L., Gajo, O., Kirsh, M. M., Morris, J. D. and Sloan, H. E.: The Reversibility of Acute Ischemic Injury to the Myocardium by Restoration of Coronary Flow. J. Thorac. Cardiovasc. Surg., 64:840, 1972.
27. Page, D. L., Caulfield, J. B., Kastor, J. A., DeSanctis, R. W. and Sanders, C. A.: Myocardial Changes Associated with Cardiogenic Shock. N. Engl. J. Med., 285:133, 1971.
28. Powell, W. J., Daggett, W. M., Magro, A. R., Bianco, J. A., Buckley, M. J., Sanders, C. A., Kantrowitz, A. R. and Austen, W. G.: Effects of Intra-aortic Balloon Counterpulsation on Cardiac Performance, Oxygen Consumption and Coronary Blood Flow in Dogs. Circ. Res., 26:753, 1970.
29. Sanders, C. A., Buckley, M. J., Leinbach, R. C., Mundth, E. D. and Austen, W. G.: Mechanical Circulatory Assistance: Current Status and Experience with Combining Circulatory Assistance, Emergency Coronary Angiography and Acute Myocardial Revascularization. Circulation, 45:1292, 1972.
30. Scanlon, P. J., Nemickas, R., Tobin, J. R., Jr., Anderson, W., Montoya, A. and Pifarre, R.: Myocardial Revascularization during Acute Phase of Myocardial Infarction. JAMA, 218:207, 1971.
31. Scheidt, S., Ascheim, R. and Killip, T.: Shock after Acute Myocardial Infarction. A Clinical and Hemodynamic Profile. Am. J. Cardiol., 26:556, 1970.
32. Smullens, S. N., Wiener, L., Kasparian, H., Brest, A. N., Bacharach, B., Noble, P. H. and Templeton, J. Y.: Evaluation and Surgical Management of Acute Evolving Myocardial Infarction. J. Thorac. Cardiovasc. Surg., 64:495, 1972.
33. Sustaita, H., Chatterjee, K., Matloff, J. M., Marby, A. T., Swan, H. J. C. and Fields, J.: Emergency Bypass Surgery in Impending and Complicated Acute Myocardial Infarction. Arch. Surg., 105:30, 1972.
34. Sustaita, H., Chatterjee, K., Matloff, J. M. and Swan, H. J. C.: The Rationale for Surgery in Preinfarction Angina. Am. J. Cardiol. In press.
35. Swan, H. J. C., Ganz, W., Forrester, J., Marcus, H., Diamond, G. and Chonette, D.: Catheterization of the Heart in Man with Use of a Flow-directed Balloon-tipped Catheter. N. Engl. J. Med., 283:447, 1970.
36. Wood, P.: Acute and Subacute Coronary Insufficiency. Brit. Med. J., 2:5242, 1961.
37. Cheanvechai, C., Effler, D. B., Loop, F. D., Groves, L. K., Sheldon, W. C. and Sones, F. M., Jr.: Aorta-to-Coronary Graft during Early and Late Phases of Acute Myocardial Infarction. Ann. Thorac. Surg. In press.

Discussion

Dr. J. M. Matloff (Los Angeles): Our experience at the Cedars-Sinai Medical Center with similar types of patients has been based on a somewhat different protocol in that we have felt that early, direct revascularization surgery has the most to offer. As soon as these patients are identified, they are taken directly to the catheterization laboratory and then to surgery without taking the time to institute mechanical support along the way.

Can I have the first slide, please. We have now seen 86 patients in our COU with preinfarction angina. Identical criteria were used to define these patients. They have been separated into two *non-randomized* groups, as a function of the mode of therapy chosen. Twenty-nine were treated medically by a number of physicians; there were 11 deaths within one month of hospital admission for a mortality of 38%. Overall, 57 patients had their preinfarction state terminated by surgery. There were 3 deaths (5%) in this group. Twenty-one of the 57 patients treated surgically were considered to be complicated by virtue of occurrence of a major complication prior to the time they were operated; they experienced 28 instances of progression to infarction with continuing pain, ventricular fibrillation or tachycardia, complete heart block, congestive heart failure or hypotension. This group is thus comparable to the type of complicated patient that Dr. Mundth has identified. Two of our three surgical deaths were in this group.

In regard to patients in cardiogenic shock; we have now operated 12 such patients. Eight patients had no other mechanical defect than the large akinetic area corresponding to their acute ischemia. Each of these 8 had at least a left anterior descending aortocoronary vein bypass graft without resection of the infarct. The 6 who survived were operated within four hours of the onset of shock. There were 4 other patients who had been in shock for much longer periods of time, up to two weeks; these 4 each developed a mechanical defect 3 to 7 days after their acute infarction and the onset of shock coincided with the development of this hemodynamic burden. Despite combinations of infarctectomy, aneurysmectomy, mitral valve replacement and bypass, there were no survivors in this group. (Slide) Not only is survival influenced by how soon these patients are operated, but postoperative left ventricular functional status is also influenced. If we look at left ventricular function as measured by calculation of ejection fraction preoperatively and postoperatively, we have noted that in patients with normal preoperative function it can be anticipated that function will be normal postoperatively. Similarly, those with depressed preoperative function will improve significantly after successful surgery. These findings hold *only* if the patient does not experience acute infarction either just prior to or during surgery; in the latter instances the patient may survive but his left ventricular function is much worse postoperatively. Obviously, this is also true of the patient with infarction and shock who is bypassed and survives. (Slide off).

On the basis of these experiences we are encouraged to be very aggressive with early revascularization in patients with acute cardiac ischemia. Such therapy seems to have significant advantages in relation to survival and to preservation of left ventricular function.

Dr. David C. Sabiston, Jr. (Durham): Dr. Mundth and his colleagues are to be congratulated on these fine and innovative studies. Moreover, the manuscript contains much additional data which add further to the importance of this work.

At present, the most frequent indication for myocardial revascularization is intractable angina pectoris. In the data which you have just heard, a series of 110 patients with serious and critical complications of myocardial infarction in addition to angina are reviewed. The authors are to be especially commended for making the series all inclusive since its initiation. I should like to confine my remarks to one aspect of the problem, that is those patients with myocardial infarction and intractable shock.

It is now well recognized that prior to the development of coronary care units the mortality of patients with acute myocardial infarction who actually reached the hospital was about 30%. The role of the coronary care unit in reducing this death rate by approximately 50% in nearly all centers has been impressive. An analysis of the patients whose lives were spared shows that they were primarily those with serious arrhythmias which formerly caused death. Today, the majority of these patients, primarily as a result of continuous monitoring, can be converted either by electric shock and/or pharmacologic therapy.

The remaining mortality of 15% is comprised primarily of those tients with *refractory shock* following acute myocardial infarc-n, which is often termed "left ventricular power failure." These patients in whom the condition simply cannot be reversed by armacologic or other non-surgical means.

Studies in our laboratory of experimental myocardial infarction n which coronary blood flow has been measured by radioactive microspheres have convinced us that coronary blood flow is considerably increased in the area of myocardial infarction during intra-aortic balloon pumping. In this study which we have just heard by Dr. Mundth, the value of this procedure is also demonstarted clinically, especially if followed by a bypass graft to the coronary artery distal to an obstruction or, in some cases, correction of an acquired ventricular septal defect or of mitral insufficiency.

An immediate survival in these patients in their series of 37% and a long-term survival of 29% is a remarkable achievement, especially in these very ill patients. These fine studies should timulate us all to a further attack upon this basic problem of ntractable shock following acute myocardial infarction, which for so long has largely resisted other therapeutic approaches.

Finally, there is a difficult question which I hope Dr. Mundth will comment upon and that concerns the possible role of randomized studies in such problems.

Dr. Watts Rankin Webb (Syracuse): Dr. Mundth, Dr. Austen and their associates are certainly to be commended on this excellent work. They have provided pioneering leadership in the management of the acutely ischemic heart. I would like to emphasize couple of their concepts.

We hoped that counter-pulsation and early revascularization and other corrective surgery would be a very major help in the patient with cardiogenic shock. This has been true, of course, in a few who have been salvaged who otherwise would have certainly died.

But the results reported here and those of our own institution have shown that this group in cardiogenic shock is a very desperate salvage group, usually with multiple vessel disease and usually with previous multiple infarctions. The patient with multiple vessel disease and his first infarction rarely dies from shock. He may die of arrhythmia but he usually does not go into shock.

Most of these people in cardiogenic shock have very little viable muscle to carry on a pumping action regardless of the corrective vascular surgery that needs to be done. Thus, the overall salvage that has been achieved here is most impressive.

On the other hand, the preinfarction group usually consists of patients with good hearts. They often will have one vessel disease, two at the most, and often without a previous infarction. These are often the younger patients showing angina for the first time or only a recent extension of some minor angina. This, I feel, is a group in which we should be much more aggressive.

Over 60% of the cardiac deaths in this country occur outside the hospital and many are in this group with relatively short premonitory periods of angina, which have been treated by standard medical measures, which may mean being considered relatively unimportant by the physician.

Indeed, these are usually the patients who die of sudden arrhythmias on the golf course, in the bank lobby, in the cold parts of the country shovelling snow or perhaps here in frustration in the smog of the Los Angeles Freeway! But we feel that in any patient the onset of the angina, or any change in angina, is an indication for a complete study and probably early revascularization. Like several others, we have found that urgent surgery for the preinfarction syndrome is safe and rewarding.

Of 26 patients that we have now seen—all proved by arteriograms to have 75% occlusion of at least one major vessel—four were not operated upon. These four had infarctions and two of them died which, if nothing else, proved the accuracy of our cardiologists in diagnosing this condition.

The other 22 underwent operation, all survived and most of them have returned to their previous occupations, One had a non-fatal infarction some 3 months later in a different vessel but his graft proved to be patent.

We feel that the use of the balloon assist in these patients with an impending infarction, as reported by Dr. Mundth, certainly adds a most useful diagnostic and therapeutic tool. Those who are relieved of ischemia are then converted to an elective status for study and possible operation at a later date. If they do not respond, immediate study and operation remain very urgent.

Our work with Dr. Sugg and Dr. Cook some years ago, showed that counter-pulsation can reduce the size of an infarction secondary to ligation of a coronary artery at least experimentally and this has been confirmed and extended by Dr. Eugene Braunwald and others.

It may well be that the next major advance will be some form of counter-pulsation, preferably non-invasive, in all patients within the very first 2 hours after suffering a myocardial infarction.

If this proves to be of the same value clinically as it is experimentally, this can preserve a great deal of viable muscle and perhaps prevent the fibrotic, non-contractile end-stage heart that we see all too often.

Dr. John Y. Templeton, III (Philadelphia): Mr. Chairman, I wish to comment briefly upon the value of myocardial metabolic studies in the surgical treatment of patients with impending, evolving or progressing myocardial infarction.

We have now operated upon some 80 patients who have been followed in this protocol at Jefferson now. Initial identification of these patients is by the criteria which Dr. Mundth has mentioned in his paper, which I think are conventional.

Myocardial metabolic studies are then done by sampling of coronary sinus blood.

Comparison of CPK's between the coronary sinus and systemic venous blood and lactate between the coronary sinus and systemic arterial blood affords one an opportunity to make an objective evaluation of the status of myocardium that we regard as being very helpful.

These studies can be done with a high degree of safety. They are done rather conveniently by our medical cardiologist in the cardiac care area and we have not noticed deleterious effects on the patients as a result.

If these studies indicate the presence of viable ischemic myocardium, then one can proceed immediately with visualization of the coronary artery and appropriate operation.

We believe this affords an objective means of selecting patients for emergency operation. It gives one the assurance that there is indeed ischemic myocardium present in which function might be expected to improve if one can repair the coronary arterial flow, but also permits one to reject as an emergency a patient who does not have objective evidence of ischemia.

Dr. E. D. Mundth (Closing): In answer to Dr. Sabiston's question, it has been difficult for us throughout this experience to organize a randomized study. In regard to internal controls, it is important to note that the majority of shock patients in our series were in stage 4 shock, defined as a wedge pressure greater than 20 mm. Hg and the product of the stroke index times the mean aortic pressure less than 1200. We have found that the expected mortality of this group is near 100%.

For example, all 16 patients not undergoing angiographic study in our early series died despite continued balloon pumping. Of the 52 patients undergoing angiographic study, 17 did not undergo operation and all died, six patients died during preparation for operation, and another two patients refused operation where the situation was deemed operable, and both died. These deaths occurred despite continued balloon pumping. The remaining nine patients were thought to be inoperable angiographically and all of these patients died. Although a controlled random study was not carried out, we feel the observed salvage in the operative group represents a significant increase in survival in this group of patients. Nevertheless, we would like to institute some randomization in selected patients to try to prove this point, particularly as related to surgical intervention at various time intervals after infarction. The answer as to how late after infarction that surgery will be effective is not known.

I would like to also point out that all patients with acute myocardial ischemia in this series, including the impending infarction group, failed to respond to aggressive medical therapy before surgical intervention was undertaken. Medical therapy in these patients included the use of short and long acting nitrates, bedrest, oxygen, morphine and in most cases, the use of beta-blockade with Propranolol. Also, the majority of patients demonstrated persistent and progressive acute myocardial ischemia which could only be controlled temporarily with balloon pumping so that definitive revascularization surgery was necessary in the majority of patients.

Dr. Templeton's experience with myocardial metabolic studi provides another important and interesting aspect of the evalu tion and selection of appropriate patients for study.

Dr. Webb's experience appears to be similar to our own and appreciate hearing about Dr. Matloff's very excellent experienc particularly with the preinfarction group.

Our general attitude regarding the use of circulatory assista is that it indeed does give us a greater margin of safety and our experience has facilitated more optimal care of this diffic group of patients.

Keflex®
cephalexin monohydrate

price reduced again*

---

a 20%-30% price reduction within 12 months*

- Reductions vary by dosage form
- 250-mg.† Pulvules® of cephalexin monohydrate reduced 24%
- Identi-Dose® (unit dose medication, Lilly) reduced 19%-23%

*Based on price reductions by Eli Lilly and Company to distributors in 1972 and 1973

†Equivalent to cephalexin

Lilly
301112

Additional information available to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

HERE Burns

When parenteral analgesia is no longer required, Empirin Compound with Codeine usually provides the relief needed.

HERE Sutures

Empirin Compound with Codeine is effective for visceral as well as soft tissue pain—provides an antitussive bonus in addition to its prompt, predictable analgesia.

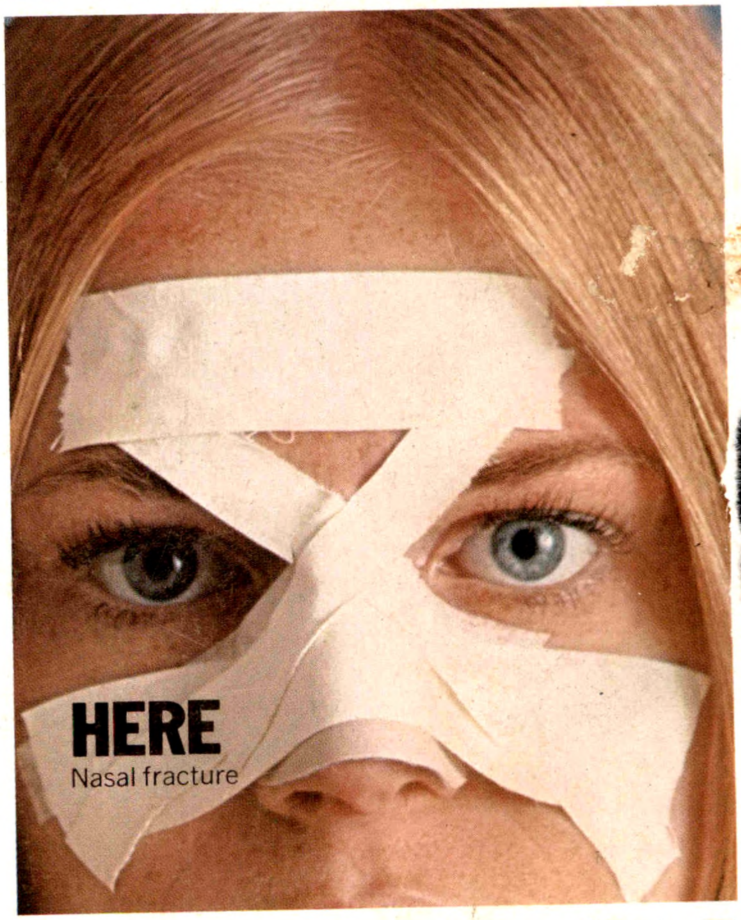
Ⓒ III **prescribing convenience:** up to 5 refills in 6 months, at your discretion (unless restricted by state law); by telephone order in many states.

Empirin Compound with Codeine **No. 3,** codeine phosphate* 32.4 mg. (gr. ½); **No. 4,** codeine phosphate* 64.8 mg. (gr. 1). *Warning—may be habit-forming. Each tablet also contains: aspirin gr. 3½, phenacetin gr. 2½, caffeine gr. ½.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

Healing nicely, but it still HURTS



EMPIRIN® COMPOUND c̄ CODEINE

#3, codeine phosphate* (32.4 mg.) gr. 1⁄
#4, codeine phosphate* (64.8 mg.) gr.